PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 417/00, A61K 31/44 | A1

(11) International Publication Number: WO 97/36901

(43) International Publication Date: 9 October 1997 (09.10.97)

(21) International Application Number: PCT/US97/05304

(22) International Filing Date: 1 April 1997 (01.04.97)

(30) Priority Data:

60/014,592	3 April 1996 (03.04.96)	US
9613462.2	27 June 1996 (27.06.96)	GB
60/022,647	24 July 1996 (24.07.96)	US
9617277.0	16 August 1996 (16.08.96)	GB

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ANTHONY, Neville, J. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). GOMEZ, Robert, P. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). GRAHAM, Samuel, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* *62*:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* *310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* *61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* *30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesyl-

ation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al., Science, 260*:1934-1937 (1993) and G.L. James *et al., Science, 260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al., Proc. Natl. Acad. Sci U.S.A., 91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al., Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al., ibid*; Casey *et al., ibid*; Schafer *et al., Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al., J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor

of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in four general classes (S. Graham, *Expert Opinion Ther. Patents*, (1995) 5:1269-1285). The first are analogs of farnesyl diphosphate (FPP), while a second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. Bisubstrate inhibitors and inhibitors of farnesyl-protein transferase that are non-competitive with the substrates have also been described. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al., ibid*; Reiss *et. al., ibid*; Reiss *et al., PNAS, 88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al., Science, 260*:1934-1937 (1993); Graham, et al., *J. Med. Chem., 37*, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

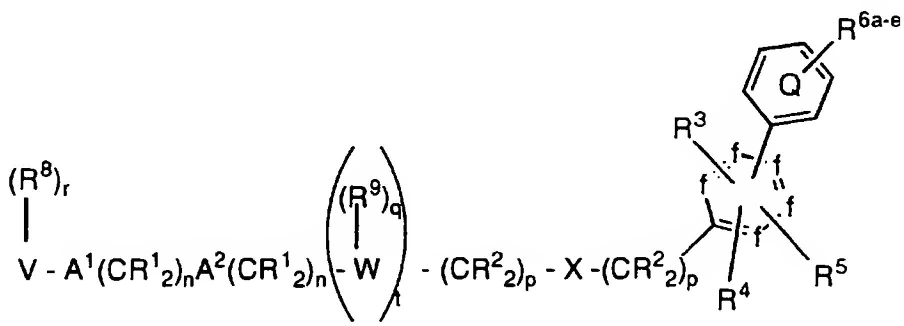
It is, therefore, an object of this invention to develop

low molecular weight compounds that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises arylheteroaryl-containing compounds which inhibit the farnesyl-protein transferase. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

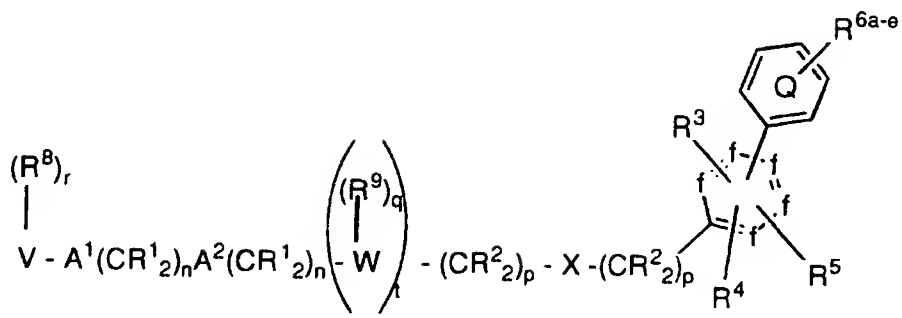
The compounds of this invention are illustrated by the formula A:



A

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



A

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-,

$R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

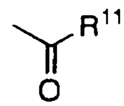
c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,

f) $-SO_2R^{11}$,
g) $N(R^{10})_2$ or
h) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,
b) aryl, substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^9 is independently selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{11}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

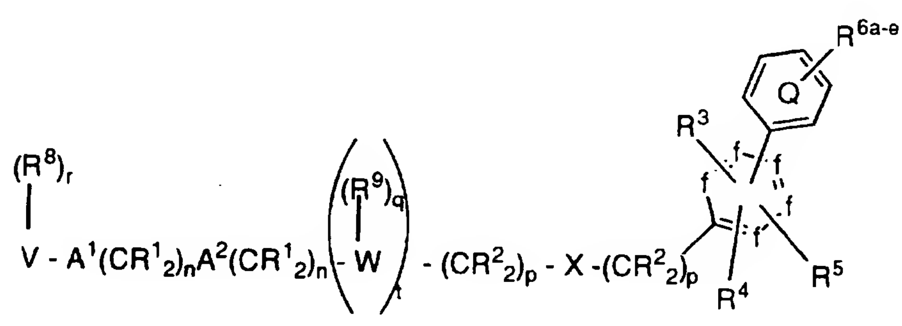
W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^{7}C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{7}C(O)-, -NR^7-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- or -S(=O)$_m$-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention is illustrated by the following formula A:



A

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is independently selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl;
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl;

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

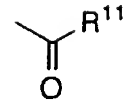
R^7 is selected from: H; $C_{1\text{-}4}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) $C_{1\text{-}4}$ alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f) $-SO_2R^{11}$,

g) $N(R^{10})_2$ or

h) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{11}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

X is a bond, O, -C(=O)-, -CH=CH-, -C(O)NR^7-, -NR^{7}C(O)-, -NR^7-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- or -S(=O)$_m$-;

m is 0, 1 or 2;

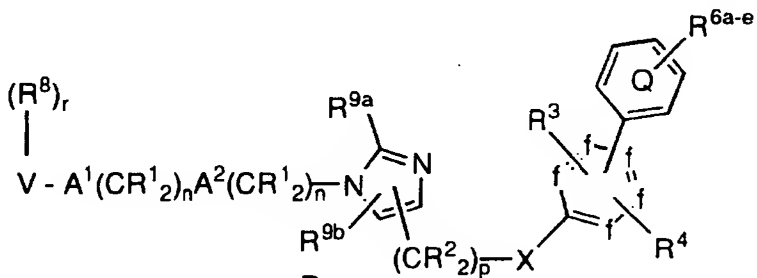
n is independently 0, 1, 2, 3 or 4;

p is independently 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula B:



B

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl,

2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

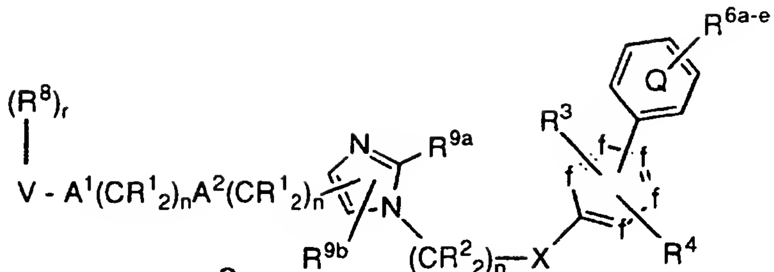
provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;
provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or the pharmaceutically acceptable salts thereof.

Another preferred embodiment of the compounds of this invention are illustrated by the formula C:



C

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

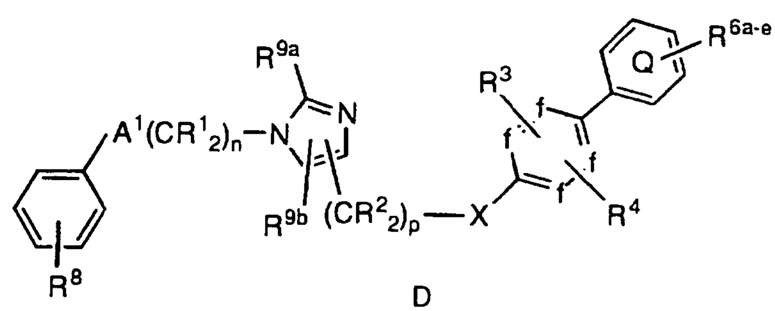
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;
provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or the pharmaceutically acceptable salts thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



D

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:
a) hydrogen,
b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

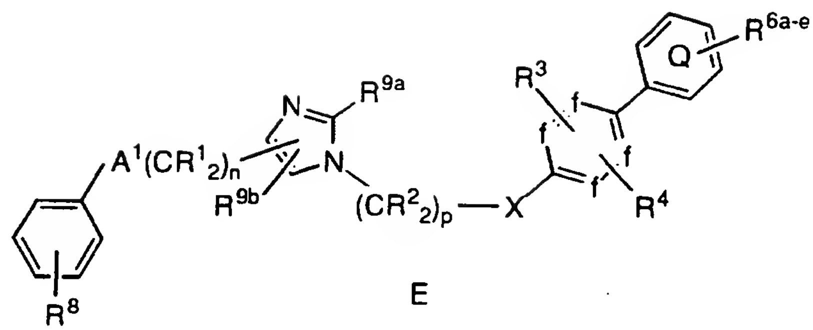
A^1 is selected from: a bond, -C(O)-, O, -$N(R^{10})$-, or $S(O)_m$;

X is a bond, -CH=CH-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, -NR^{10}-, O or -C(=O)-,

n is	0 or 1; provided that n is not 0 if A^1 is a bond, O, -$N(R^{10})$- or $S(O)_m$;
m is	0, 1 or 2; and
p is	0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:



E

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$, F or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl

ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

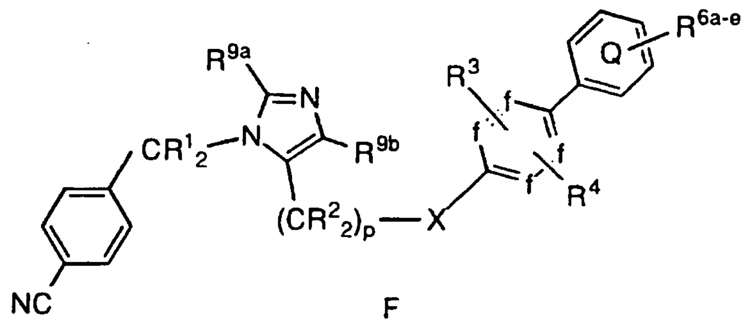
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterarył, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, -NR^{10}-, O or -C(=O)-;

n is 0 or 1;
m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;

or the pharmaceutically acceptable salts thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula F:



F

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or F,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3,

R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

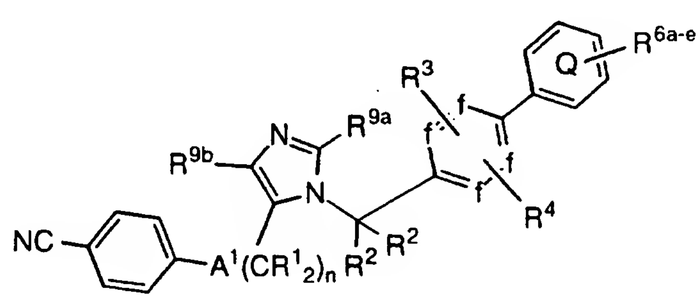
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula G:



G

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle or C_3-C_{10} cycloalkyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 a lkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or $S(O)_m$;

m is 0, 1 or 2; and
n is 0 or 1;

or the pharmaceutically acceptable salts thereof.

Preferred compounds of the invention are:

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

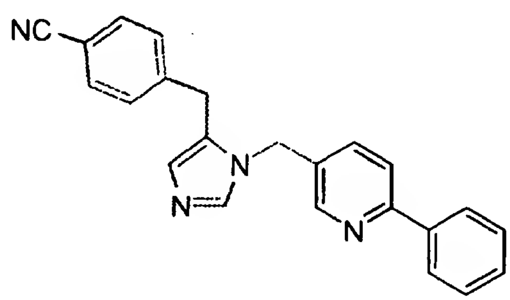
1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole and

1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

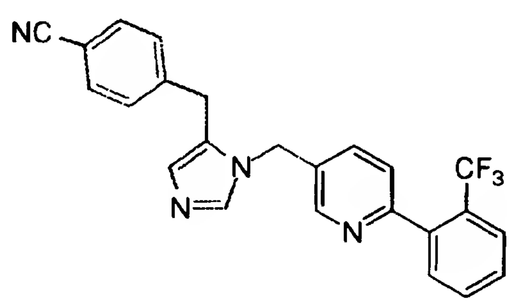
or a pharmaceutically acceptable salt thereof.

Specific examples of the compounds of the instant invention are:

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole



1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole



or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical

isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^1, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" and the alkyl portion of aralkyl and similar terms, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

"Alkenyl" groups include those groups having the specified number of carbon atoms and having one or several double bonds. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

"Alkynyl" groups include those groups having the specified number of carbon atoms and having one triple bonds. Examples of alkynyl groups include acetylene, 2-butynyl, 2-pentynyl, 3-pentynyl and the like.

"Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl," and the aryl portion of aroyl and aralkyl, is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to

11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopyrrolidinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl,

tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

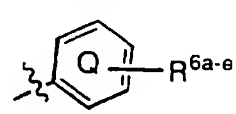
As used herein in the definition of R^3, R^4, R^5 and R^{6a-e}, the term "the substituted group" is intended to mean a substituted C_{1-8} alkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted aryl or substituted heterocycle from which the substituent(s) R^3, R^4, R^5 and R^{6a-e} are selected.

As used herein in the definition of R^7, the substituted C_{1-8} alkyl, substituted C_{3-6} cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroaryl-sulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

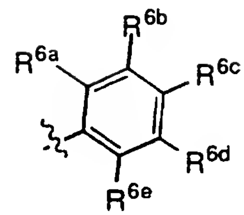
As used herein, when no specific substituents are set forth, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted on a substitutable ring carbon atom with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6\ alkyl)_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)$S(O)_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C_1-C_{20} alkyl.

Lines drawn into the ring systems from substituents (such as from R^3, R^4, Q etc.) means that the indicated bond may be attached to any of the substitutable ring carbon atoms.

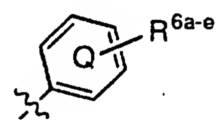
The substituent illustrated by the structure



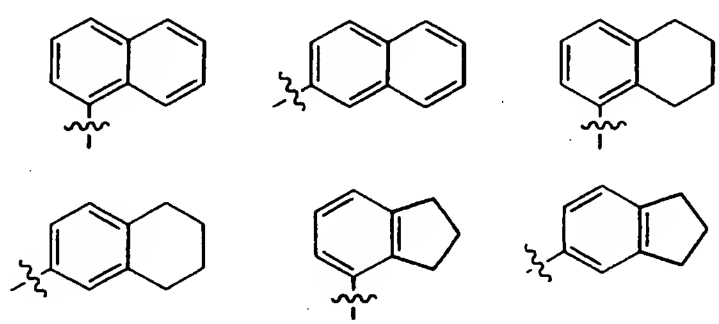
is a simplified representation of a phenyl ring having five (5) substituents (hydrogens and/or non-hydrogens) and may also be represented by the structure



The moiety described as

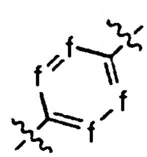


where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH, -CH=CH-CH-, -(CH2)4- and -(CH2)4- includes the following structures:

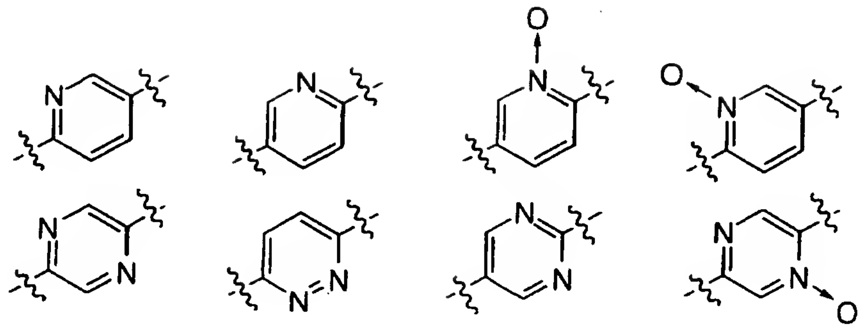


It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

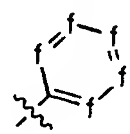
The moiety designated by the following structure



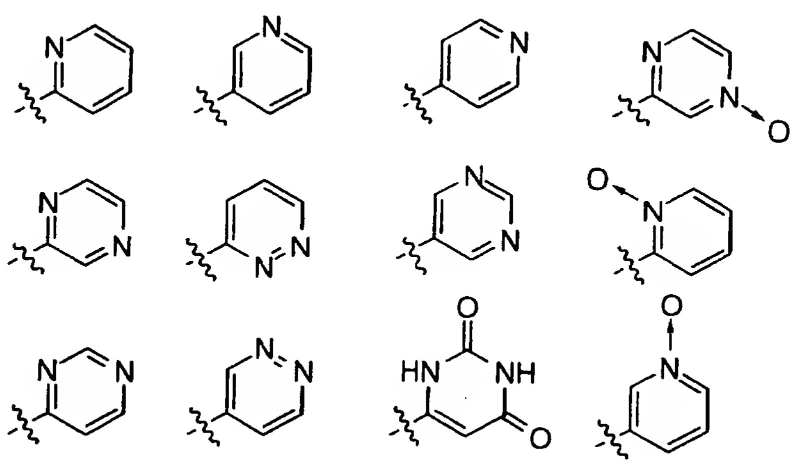
represents an aromatic 6-membered heterocyclic ring and includes the following ring systems:



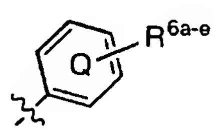
The moiety designated by the following structure



represents an aromatic 6-membered heterocyclic ring and includes the following ring systems:



wherein it is understood that one of the ring carbon atoms is substituted with



Preferably, the aromatic 6-membered heterocyclic ring is a pyridyl ring.

Preferably, R^1 and R^2 are independently selected from: hydrogen, $R^{11}C(O)O$-, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}$-, $R^{10}O$- or unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, $-N(R^{10})_2$, $R^{10}O$- and $R^{10}C(O)NR^{10}$-.

Preferably, R^3 is selected from:

a) hydrogen,
b) C_3-C_{10} cycloalkyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, CN, NO_2, $R^{10}C(O)$- or $-N(R^{10})_2$,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-.

Preferably, R^4 is selected from: hydrogen, halogen, trifluoromethyl, trifluoromethoxy and C_1-C_6 alkyl.

Preferably, R^5 is hydrogen.

Preferably, R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,
b) C_3-C_{10} cycloalkyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, CN, NO_2, $R^{10}C(O)$- or $-N(R^{10})_2$,
c) unsubstituted C_1-C_6 alkyl;
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, C_3-C_{10} cycloalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)$- or $-N(R^{10})_2$; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-.

Preferably, R^8 is independently selected from:

a) hydrogen, and

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 perfluoroalkyl or CN.

Preferably, R^9 is hydrogen, halogen, CF_3 or methyl.

Preferably, R^{10} is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)2N(R^{10})- and-N(R^{10})S(O)2-.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

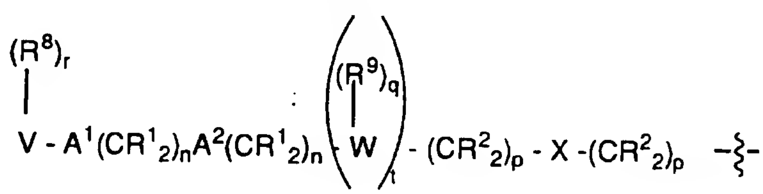
Preferably, W is selected from imidazolinyl, imidazolyl, oxazolyl, pyrazolyl, pyyrolidinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

Preferably, n and r are independently 0, 1, or 2.

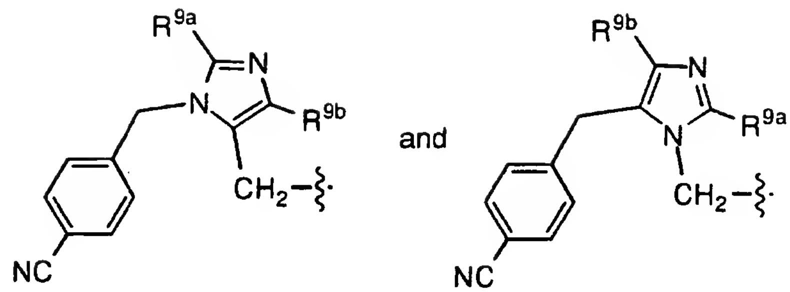
Preferably s is 0.

Preferably t is 1.

Preferably, the moiety



is selected from:



It is intended that the definition of any substituent or variable (e.g., R^1, R^2, R^9, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-21, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritsky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 1-21:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 1-12 illustrate synthesis of the instant aryl-heteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 1, for example, a arylheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted phenyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated nicotinic acid, such as 4-bromonicotinic acid, to provide the arylheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the

intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 2-4 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 1. Thus, Scheme 2 illustrates the analogous series of arylheteroaryl alcohol forming reactions starting with the methyl nicotinate boronic acid and the "terminal" phenyl moiety employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 3.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the arylheteroaryl component of the instant compounds, as shown in Scheme 4. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted heteroaryl halide in the presence of nickel (II) to provide the arylheteroaryl VII. The heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 5 illustrates the preparation of a suitably substituted biphenylmethyl bromide which could also be utilized in the reaction with the protected imidazole as described in Scheme 1.

As illustrated in Scheme 6, the sequence of coupling reactions may be modified such that the aryl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted phenyl boronic acid.

Scheme 7 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 8 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkyl-imidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

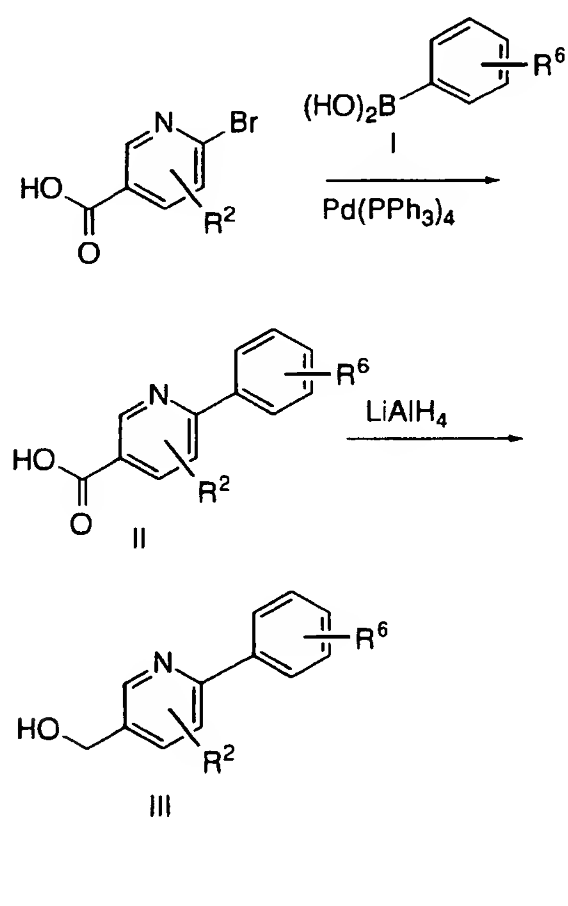
Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 9. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Scheme 10 illustrates an analogous series of reactions wherein the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted halopyridinol, such as 3-chloro-2-pyridinol, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a aryl moiety by Suzuki chemistry to provide the instant compound.

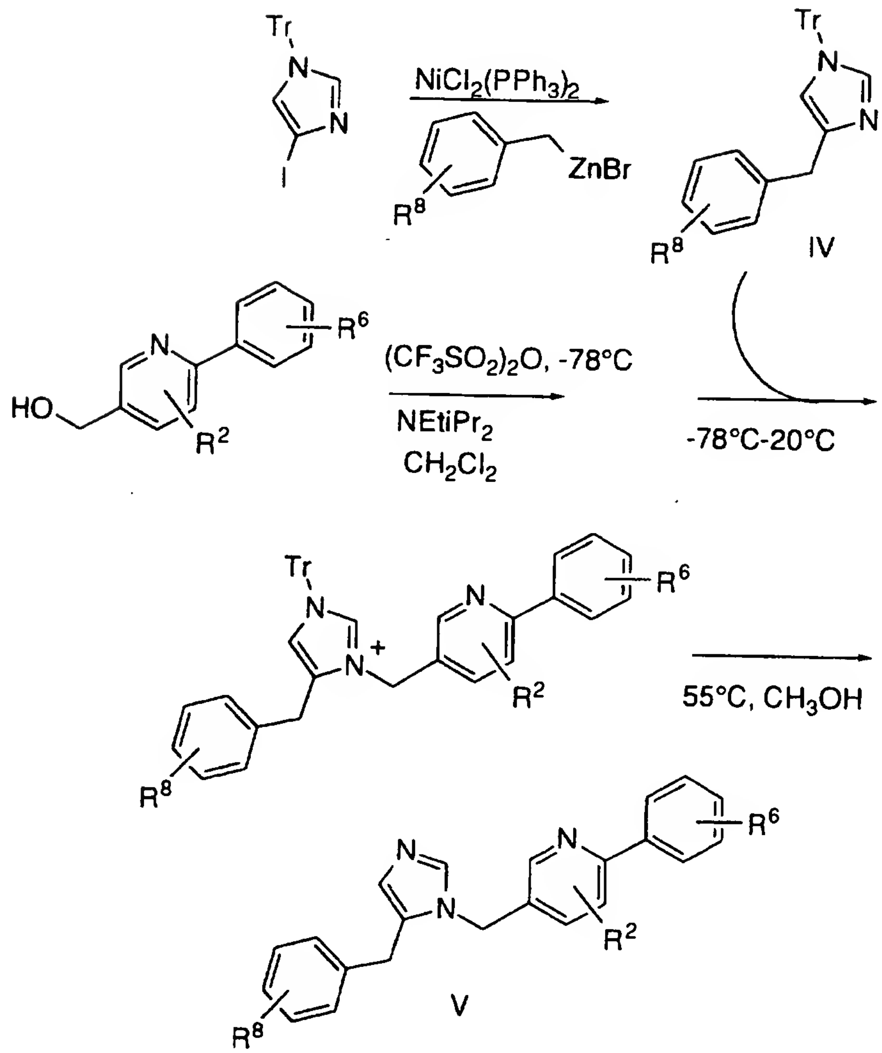
Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 11. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 1) provides the instant compound XX. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Addition of various nucleophiles to an imidazolyl aldehyde may also be employed to form a substituted alkyl linker between the biheteroaryl and the preferred W (imidazolyl) as shown in Scheme 12. Thus an aryllithium can be reacted with pyridine to form the 2-substituted N-lithio-1,2-dihydropyridine XXa. Intermediate XXa can then react with a aldehyde to provide a suitably substituted instant compound. Similar substituent manipulation as shown in Scheme 11 may be performed on the fully functionalized compound which incorporates an R^2 hydroxyl moiety.

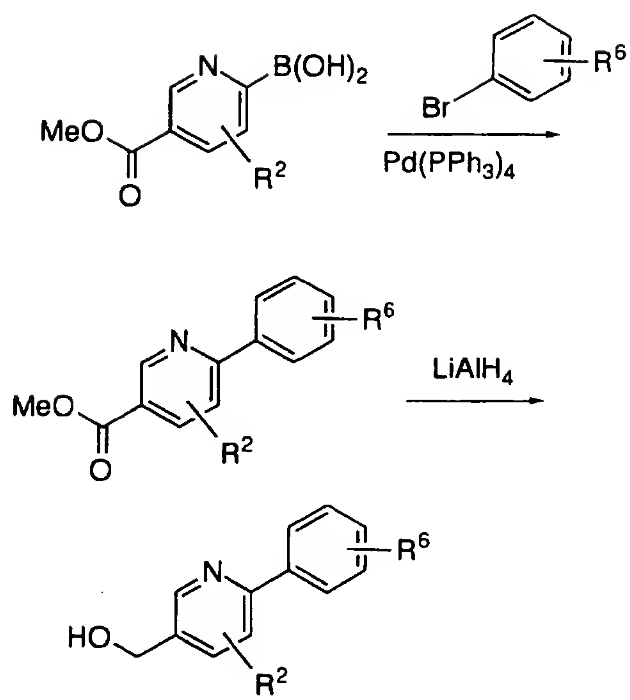
SCHEME 1



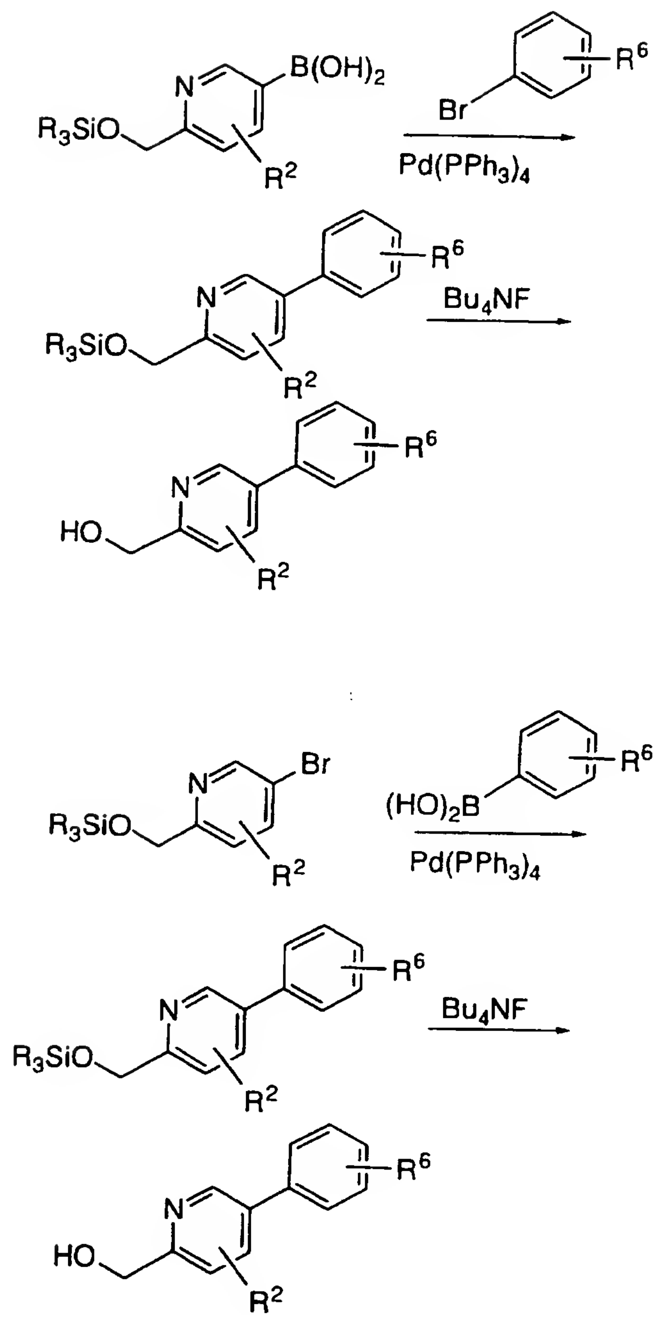
SCHEME 1 (continued)



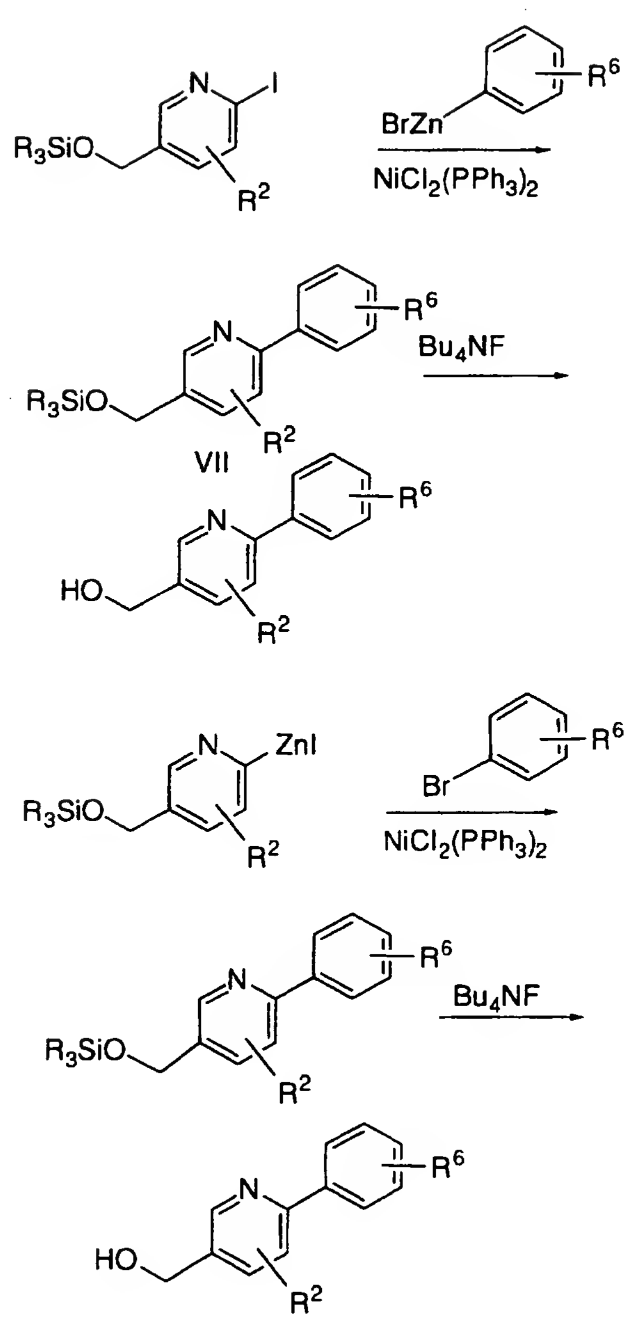
SCHEME 2



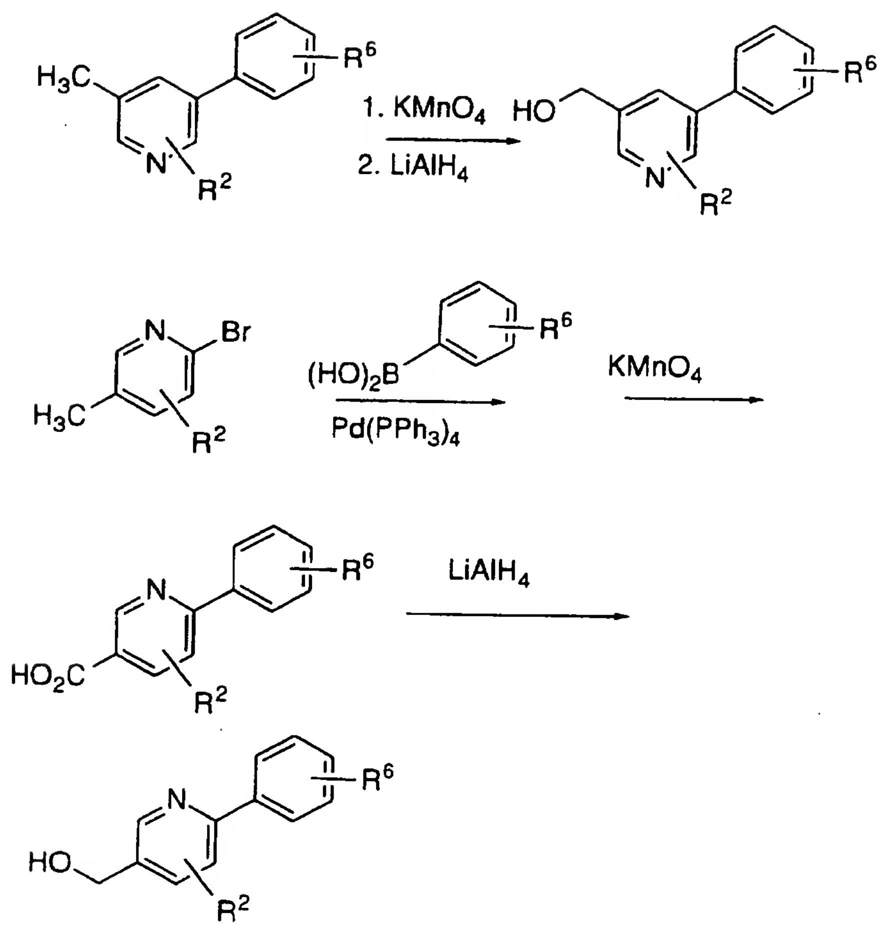
SCHEME 3



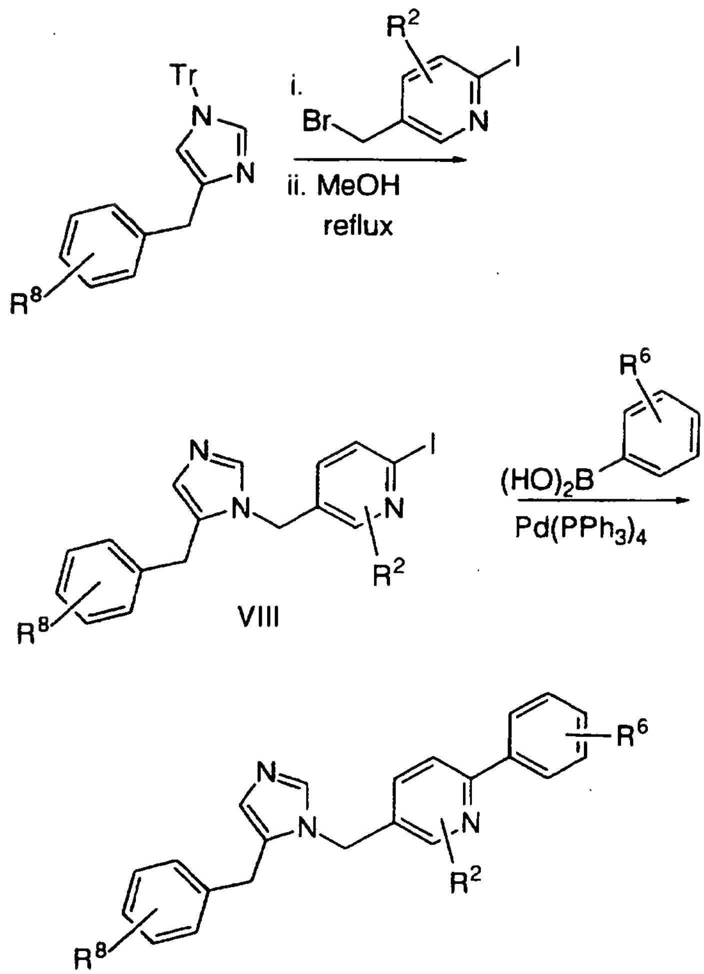
SCHEME 4



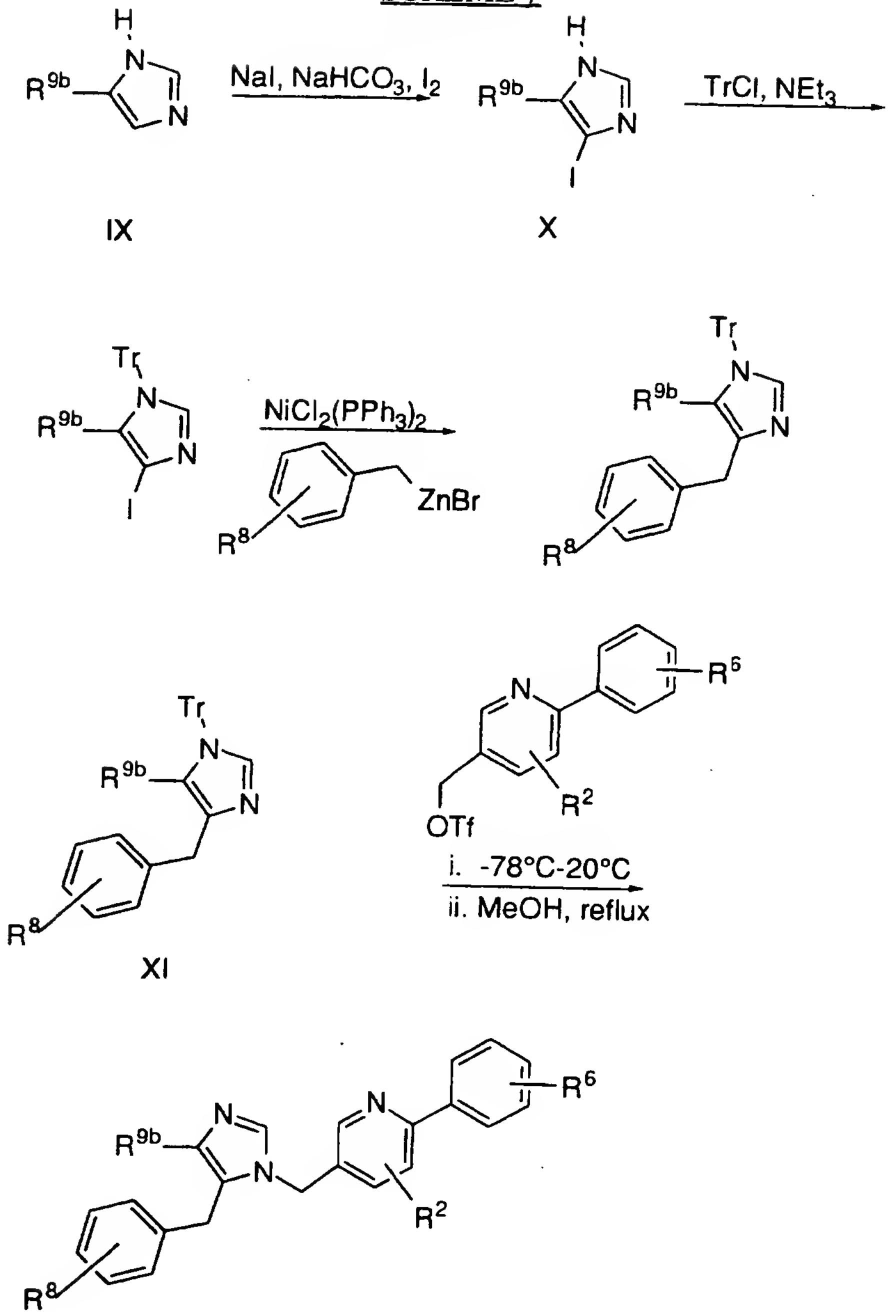
SCHEME 5


H3C
R6
R2
N
1. KMnO4
2. LiAlH4
HO
R6
N
R2
N
Br
H3C
R2
(HO)2B
R6
Pd(PPh3)4
KMnO4
N
R6
HO2C
R2
LiAlH4
N
R6
HO
R2

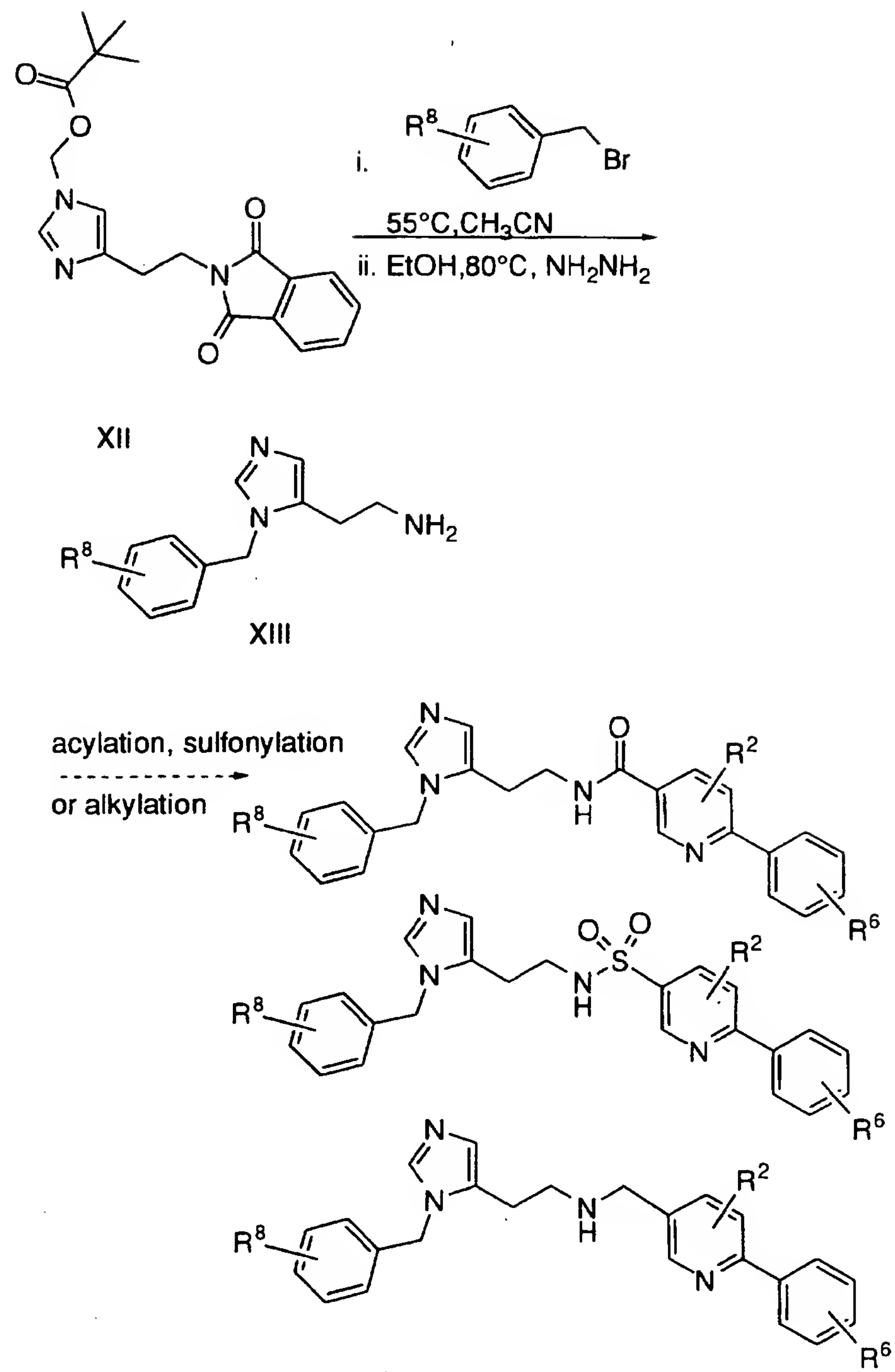
SCHEME 6


Tr
N
N
R8
i.
R2
I
Br
N
ii. MeOH
reflux
N
N
I
N
R2
R8
VIII
R6
(HO)2B
Pd(PPh3)4
R6
N
N
N
R2
R8

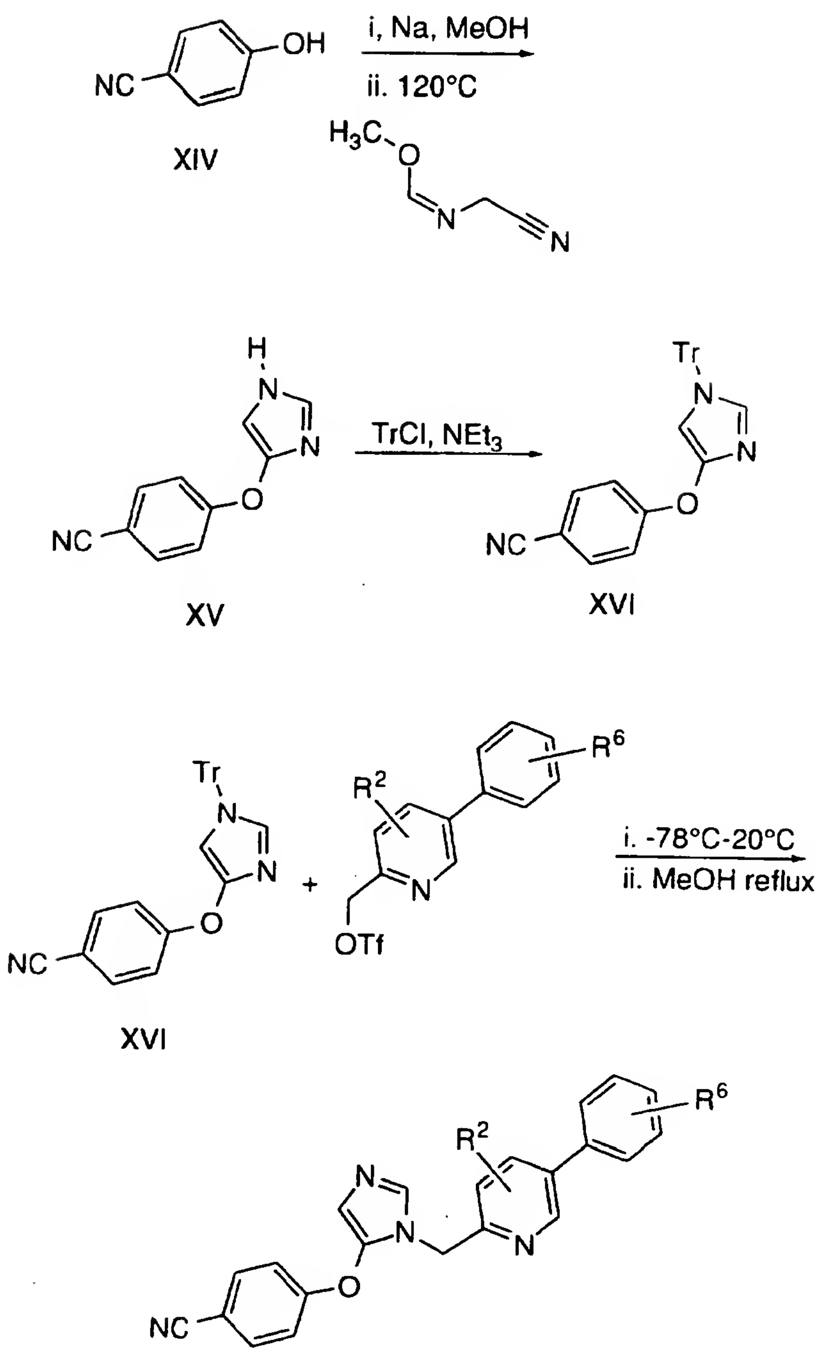
SCHEME 7


R^9b
NaI, NaHCO3, I2
TrCl, NEt3
IX
X
Tr
NiCl2(PPh3)2
ZnBr
R^8
R^6
R^2
OTf
i. -78°C-20°C
ii. MeOH, reflux
XI

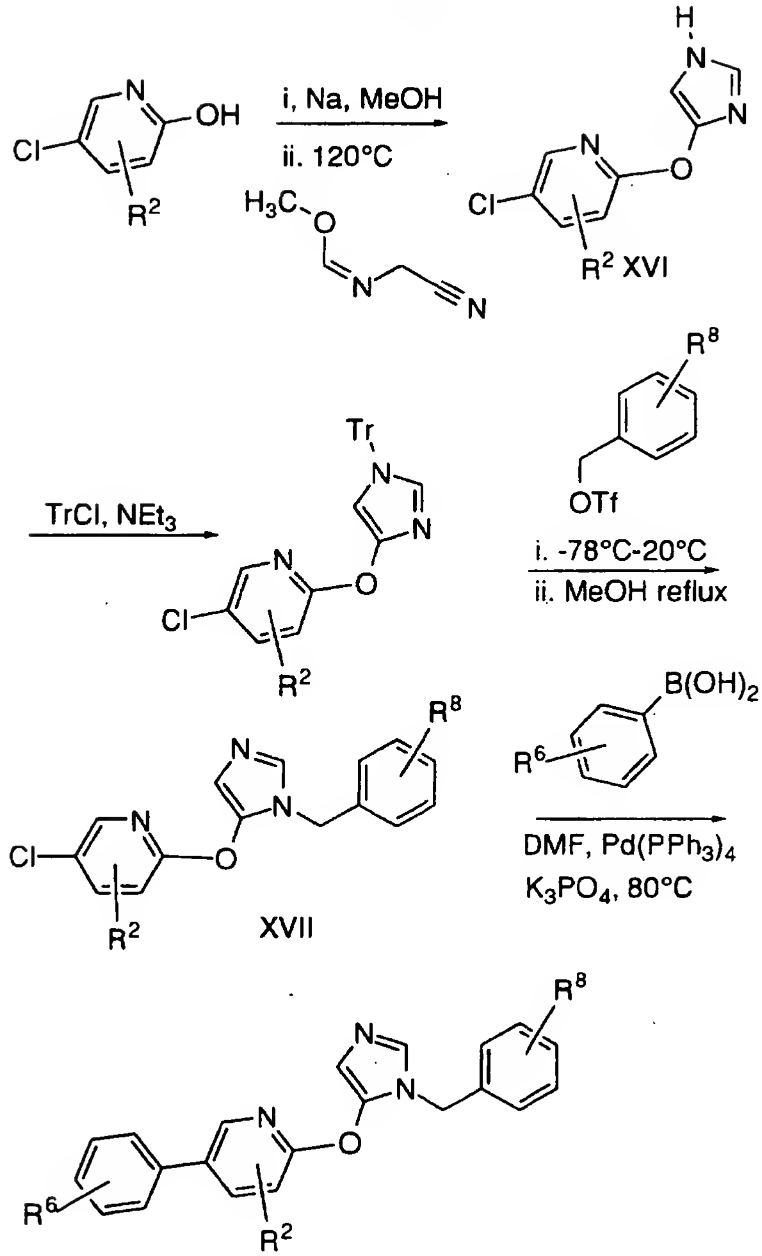
SCHEME 8


i.
R8
Br
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
XII
XIII
NH2
acylation, sulfonylation
or alkylation
R2
R6
R8

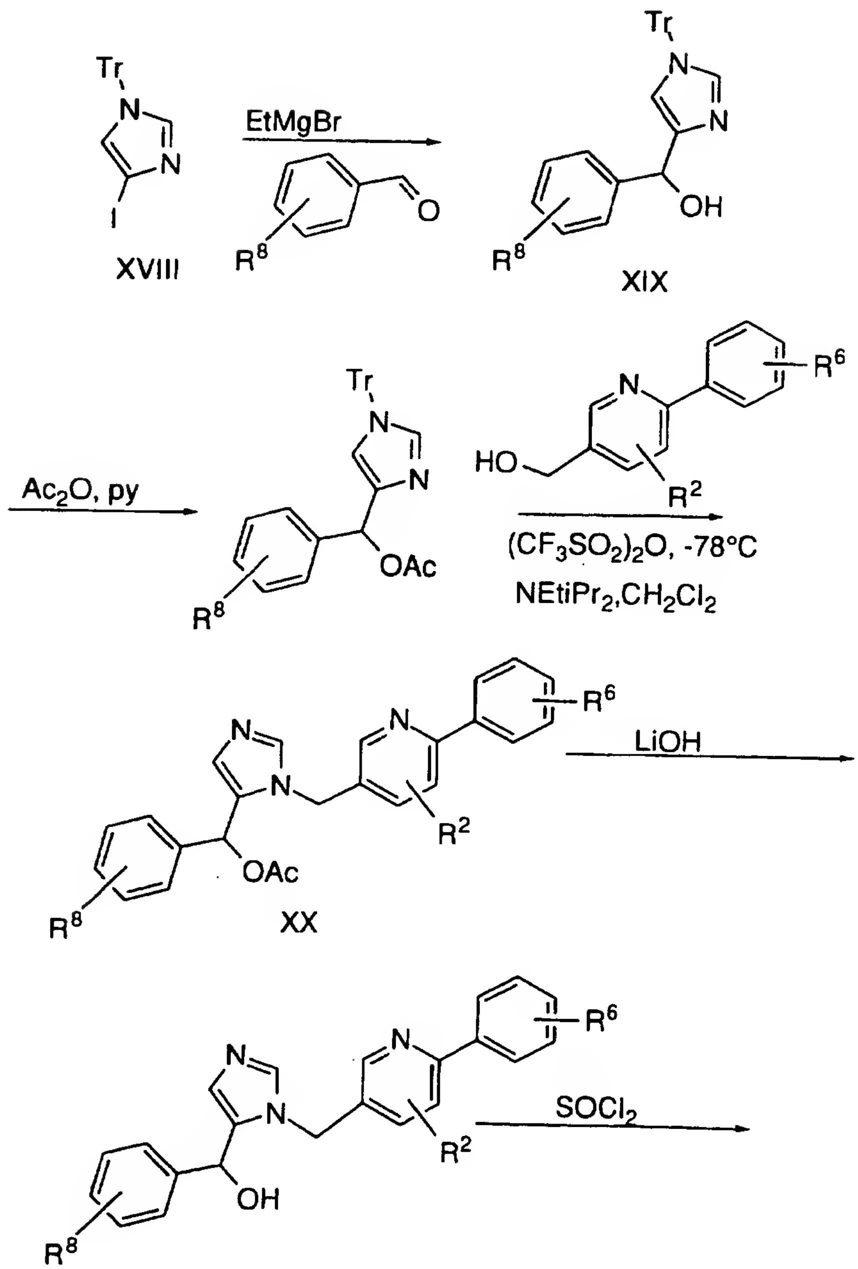
SCHEME 9


OH
NC
i, Na, MeOH
ii. 120°C
XIV
H_3C
O
N
N
H
TrCl, NEt_3
Tr
XV
XVI
R^6
R^2
OTf
i. -78°C-20°C
ii. MeOH reflux

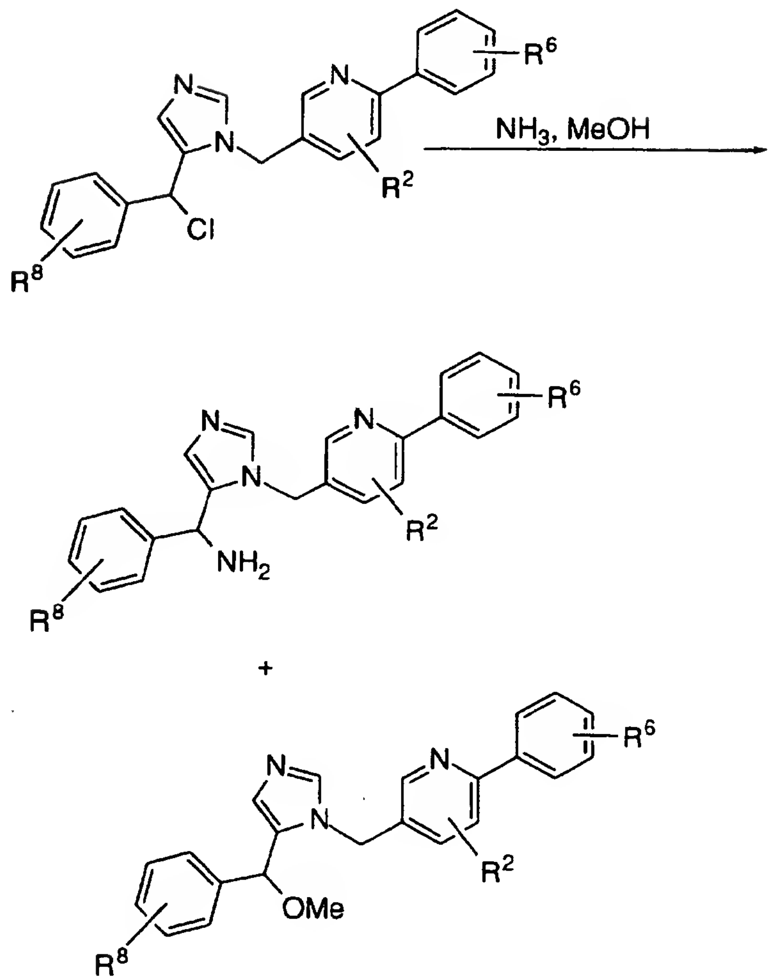
SCHEME 10


Cl
N
OH
R2
i, Na, MeOH
ii. 120°C
H3C
O
N
N
H
N
N
N
O
Cl
R2 XVI
TrCl, NEt3
Tr
N
N
N
O
Cl
R2
R8
OTf
i. -78°C-20°C
ii. MeOH reflux
B(OH)2
R6
DMF, Pd(PPh3)4
K3PO4, 80°C
R8
N
N
Cl
N
O
R2
XVII
R8
N
N
N
O
R6
R2

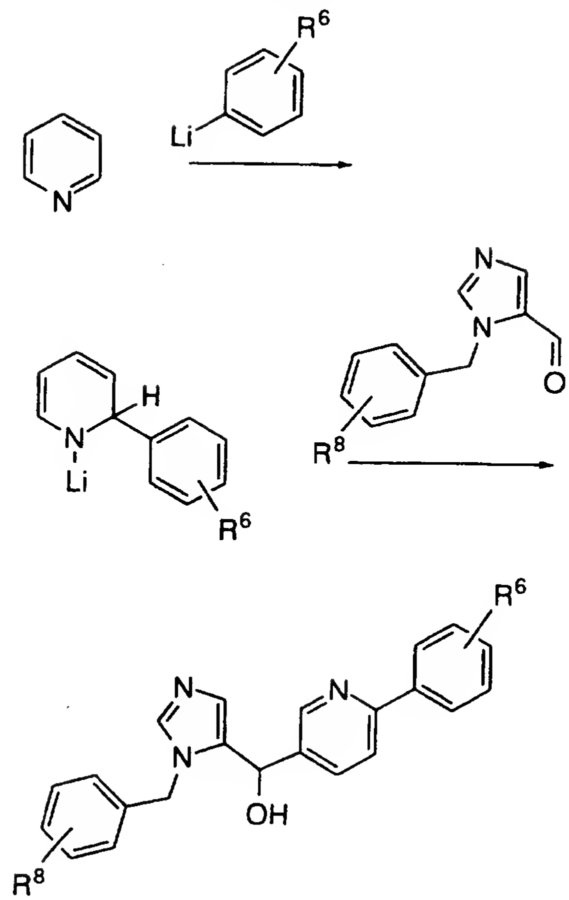
SCHEME 11


Tr
N
N
I
XVIII
EtMgBr
O
R8
OH
XIX
Ac2O, py
OAc
HO
R2
R6
(CF3SO2)2O, -78°C
NEtiPr2,CH2Cl2
LiOH
XX
SOCl2

SCHEME 11 (continued)



SCHEME 12



Schemes 13-21 illustrate reactions wherein the moiety

$$\overset{(R^8)_r}{\overset{|}{V}} - A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n\left(\overset{(R^9)_q}{\overset{|}{W}}\right)_t - (CR^1{}_2)_p\text{-}X$$

incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid. Lithioheteroaryl chemistry may be utilized, as shown in Scheme 13, to incorporate the arylheteroaryl moiety. Thus, a suitably substituted arylheteroaryl N-lithio reagent is reacted with an aldehyde to provide the C-alkylated instant compound XXI. Compound **XXI** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain XXIV. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

If the arylheteroaryl subunit reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **XXVI** in Scheme 14, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 14, 15). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as

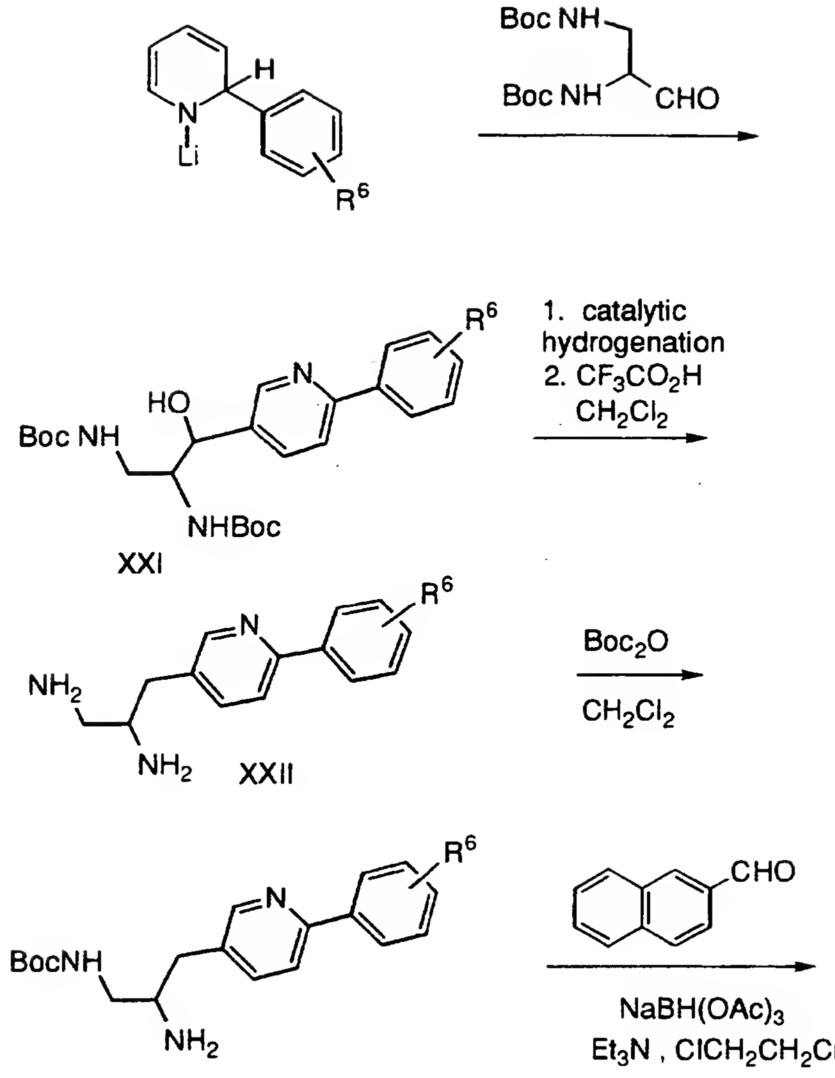
alkyl lithium reagents, to obtain secondary alcohols such as **XXX**. In addition, the fully deprotected amino alcohol **XXXI** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **XXXII** (Scheme 15), or tertiary amines.

The Boc protected amino alcohol **XXVIII** can also be utilized to synthesize 2-aziridinylmethylarylheteroaryl such as **XXXIII** (Scheme 16). Treating **XXVIII** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **XXXIII** . The aziridine is reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **XXXIV** .

In addition, the arylheteroaryl subunit reagent can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **XL**, as shown in Scheme 17. When R' is an aryl group, **XL** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **XLI**. Alternatively, the amine protecting group in **XL** can be removed, and O-alkylated phenolic amines such as **XLII** produced.

Schemes 18-21 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

SCHEME 13

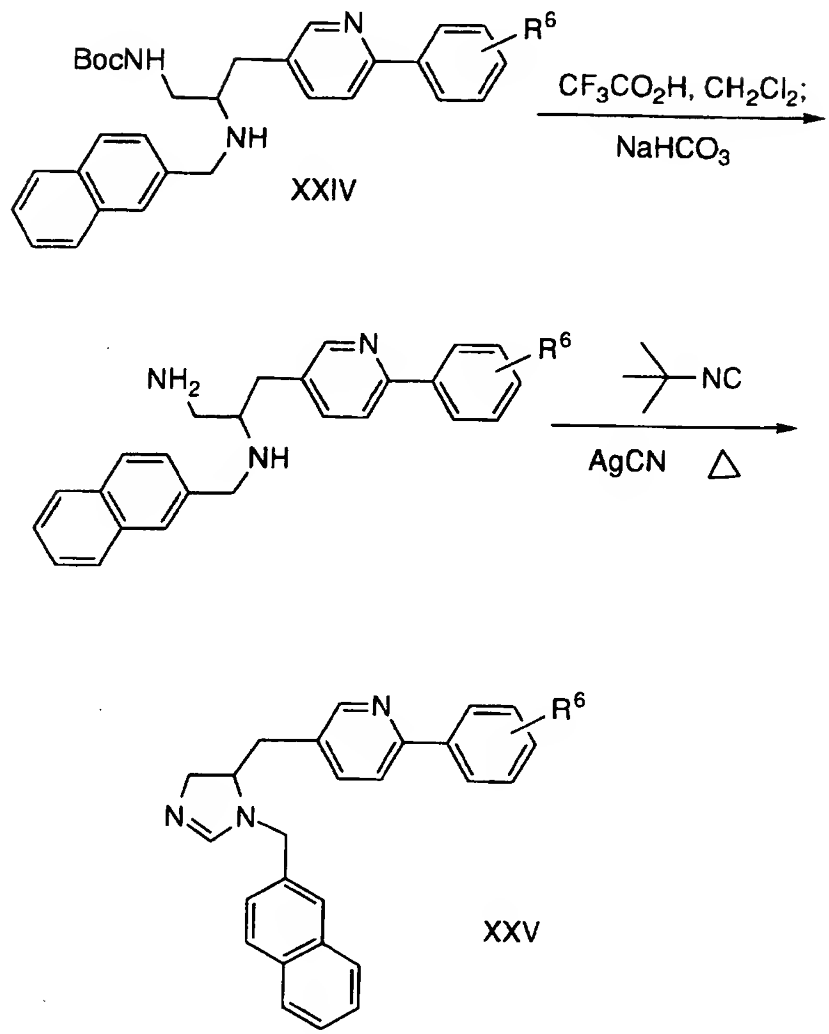


XXI

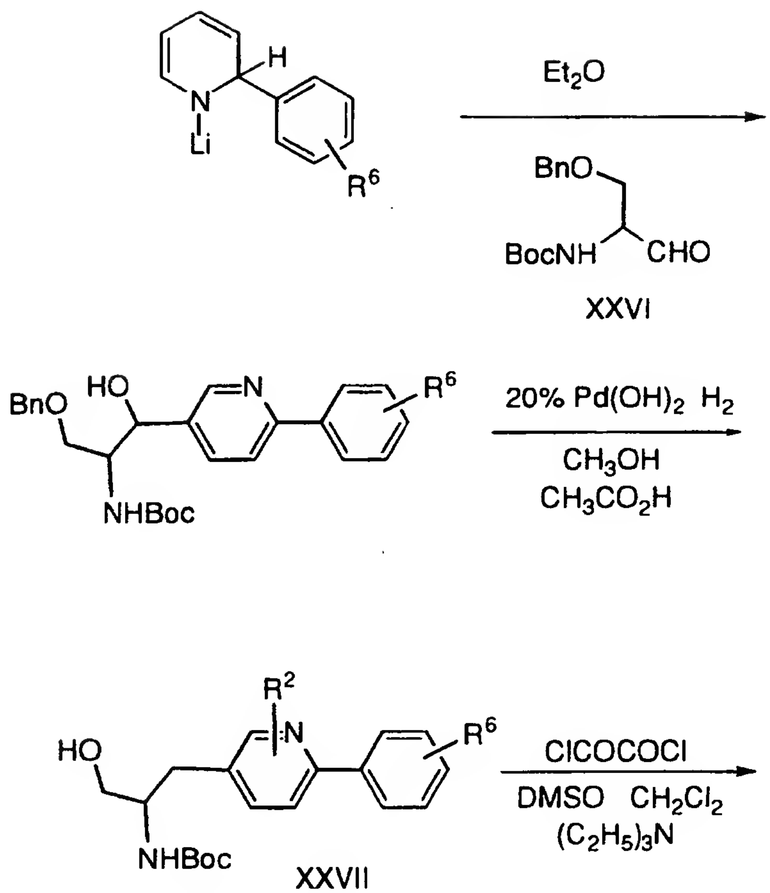
XXII

XXIII

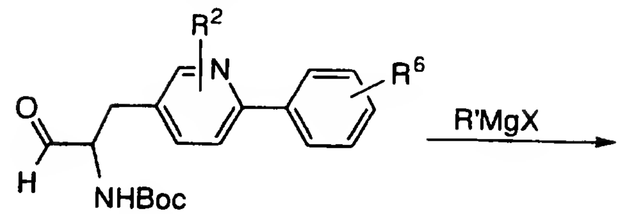
SCHEME 13 (continued)



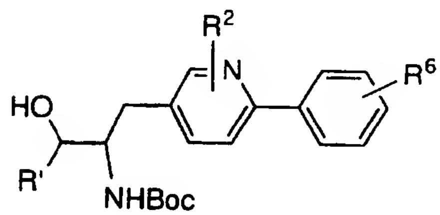
SCHEME 14


H
N
Li
R^6
Et_2O
BnO
BocNH
CHO
XXVI
BnO
HO
N
R^6
NHBoc
20% $Pd(OH)_2$ H_2
CH_3OH
CH_3CO_2H
R^2
N
HO
NHBoc
XXVII
R^6
ClCOCOCl
DMSO CH_2Cl_2
$(C_2H_5)_3N$

SCHEME 14 (continued)

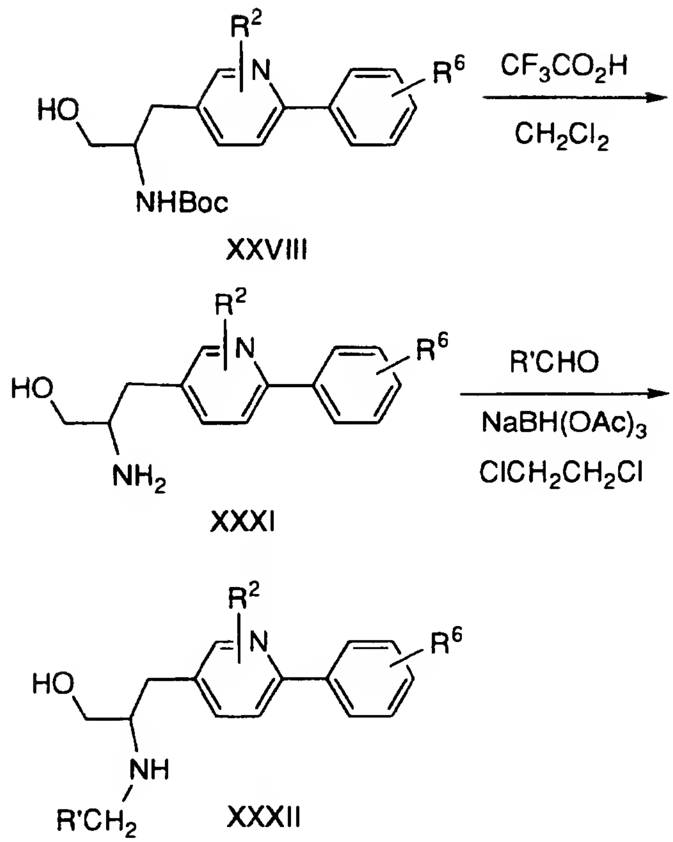


XXIX



XXX

SCHEME 15

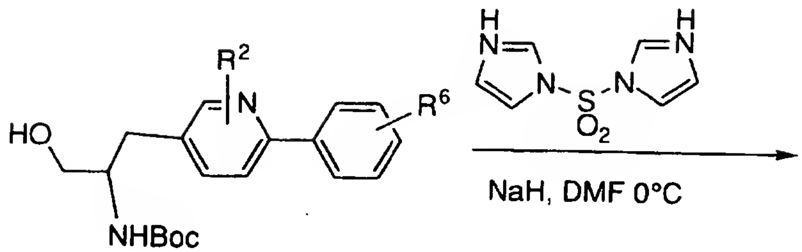


XXVIII

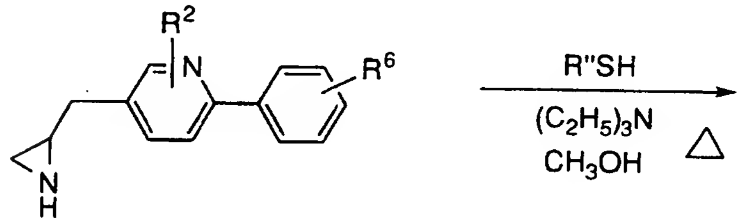
XXXI

XXXII

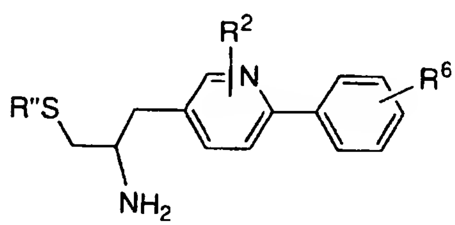
SCHEME 16



XXVIII

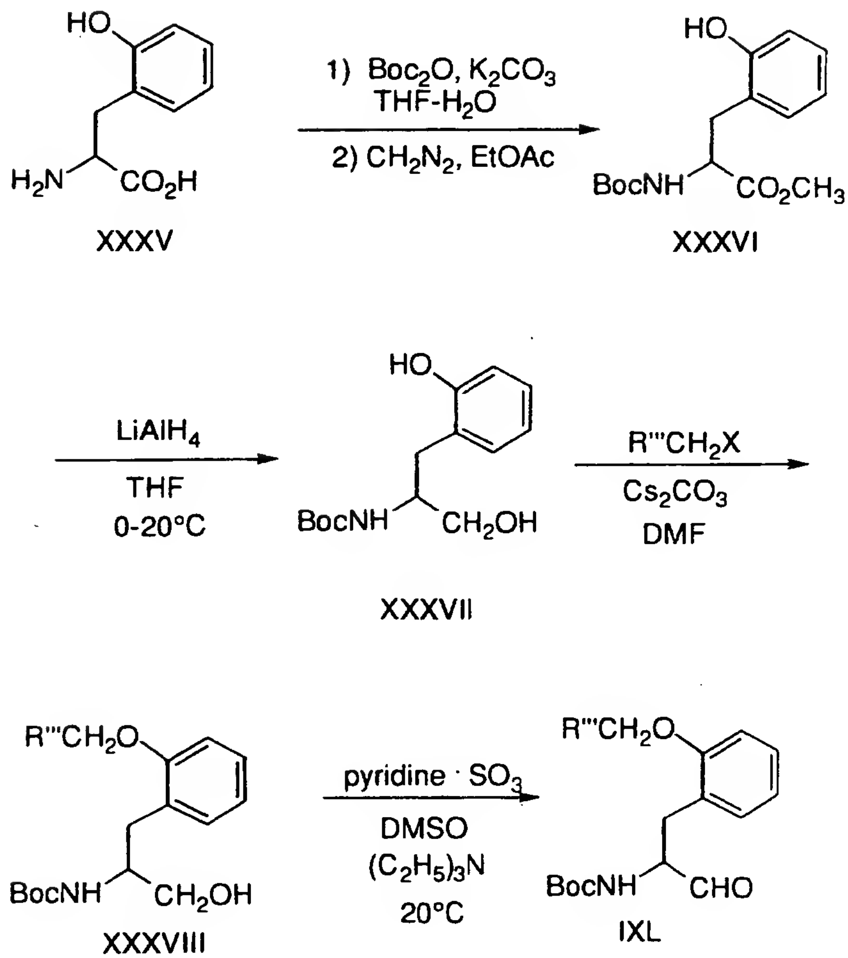


XXXIII

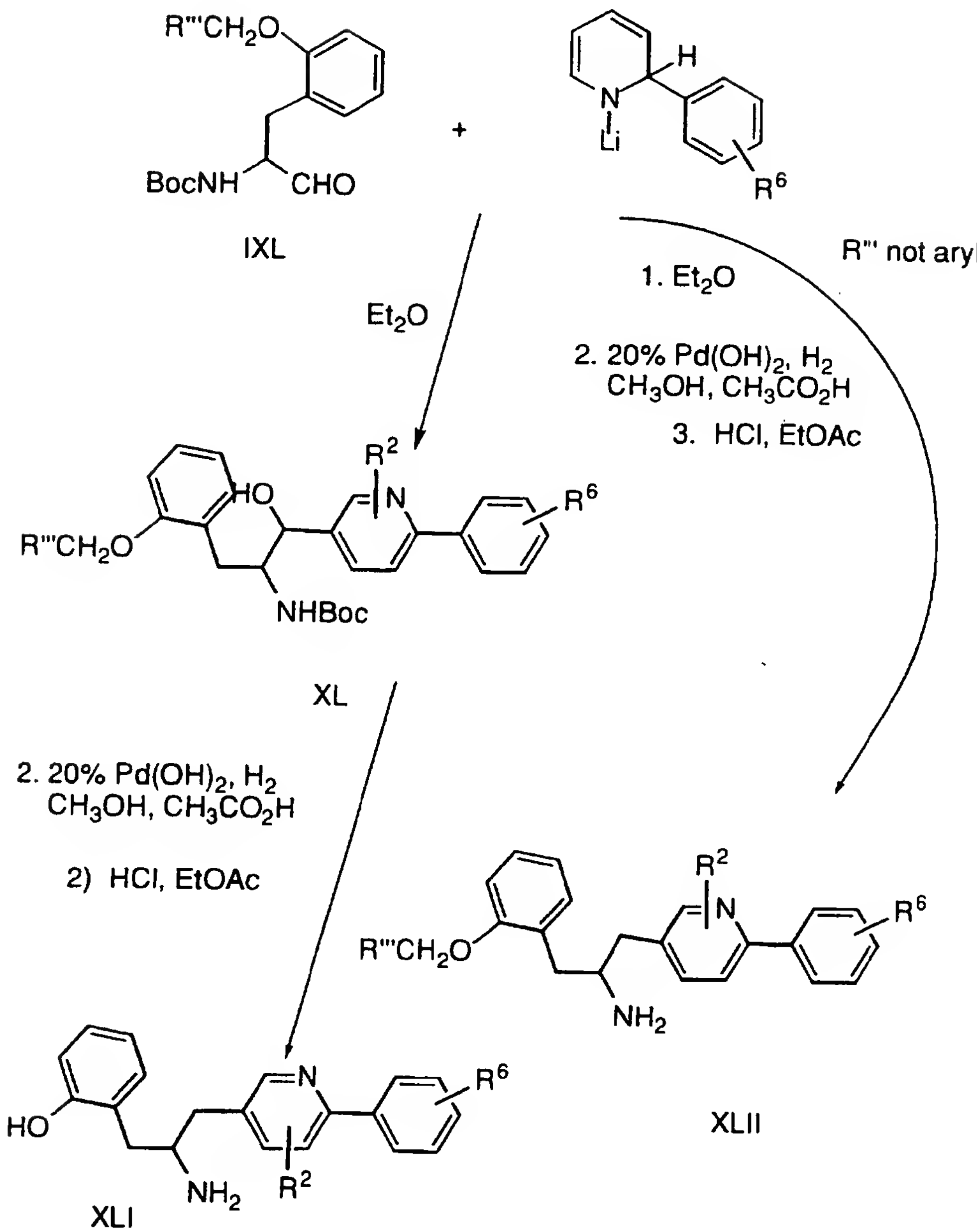


XXXIV

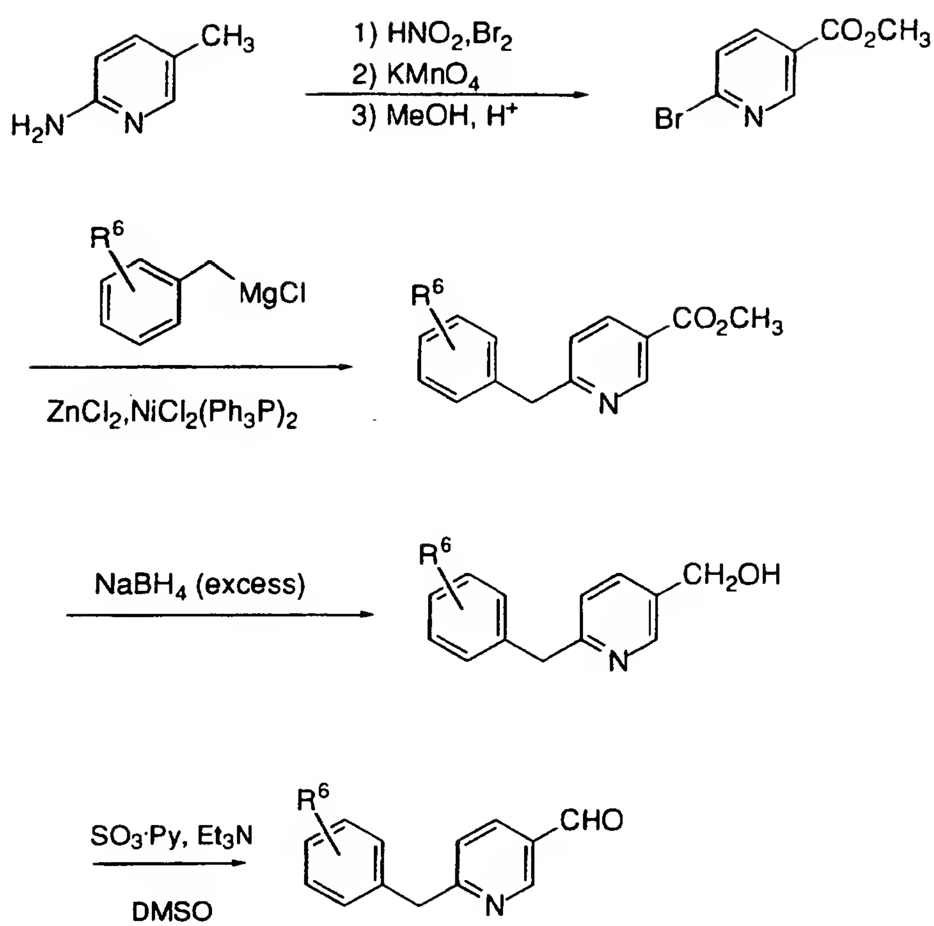
SCHEME 17


HO
H2N CO2H
XXXV
1) Boc2O, K2CO3
THF-H2O
2) CH2N2, EtOAc
HO
BocNH CO2CH3
XXXVI
LiAlH4
THF
0-20°C
HO
BocNH CH2OH
XXXVII
R'''CH2X
Cs2CO3
DMF
R'''CH2O
BocNH CH2OH
XXXVIII
pyridine · SO3
DMSO
(C2H5)3N
20°C
R'''CH2O
BocNH CHO
IXL

SCHEME 17 (continued)

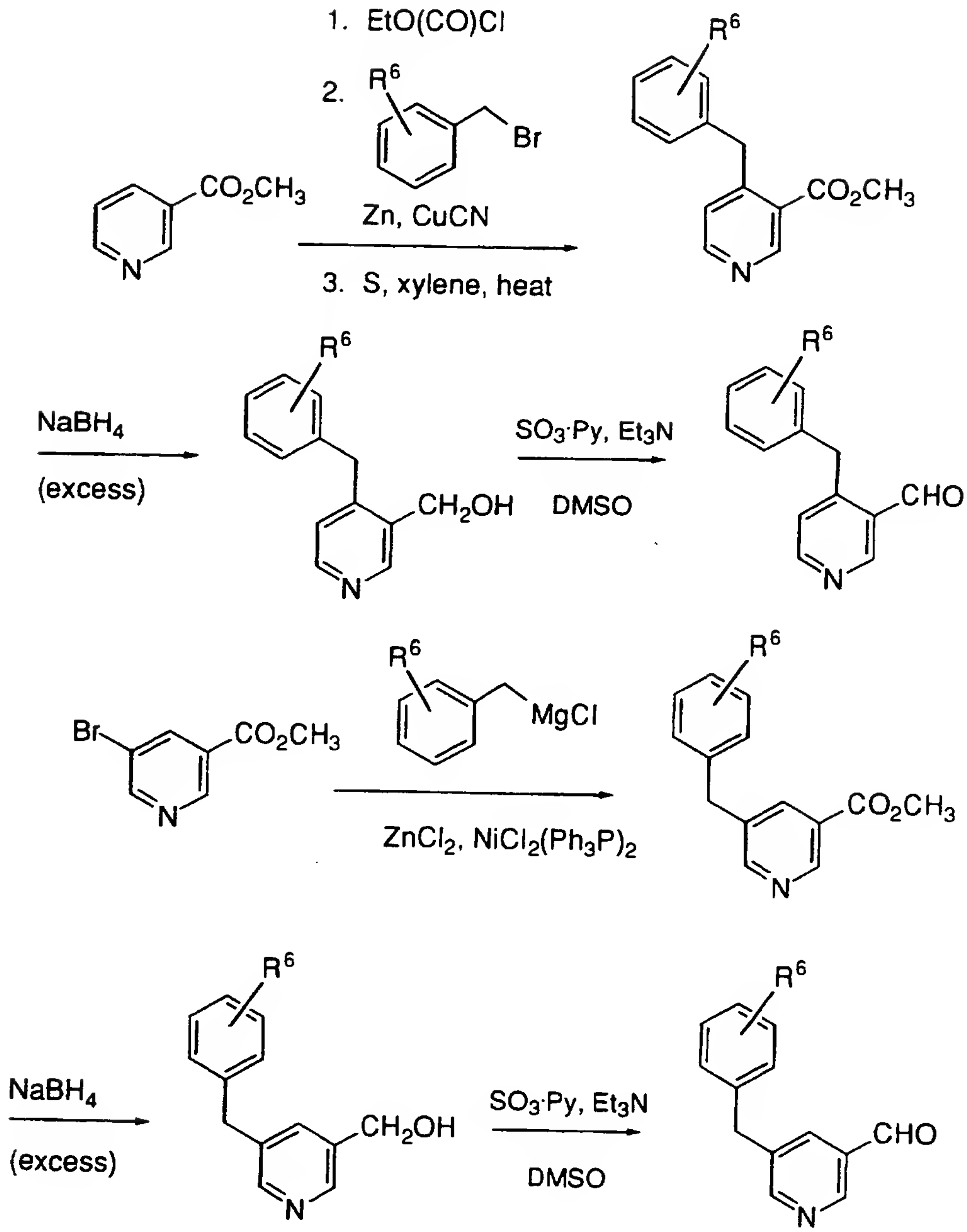


SCHEME 18

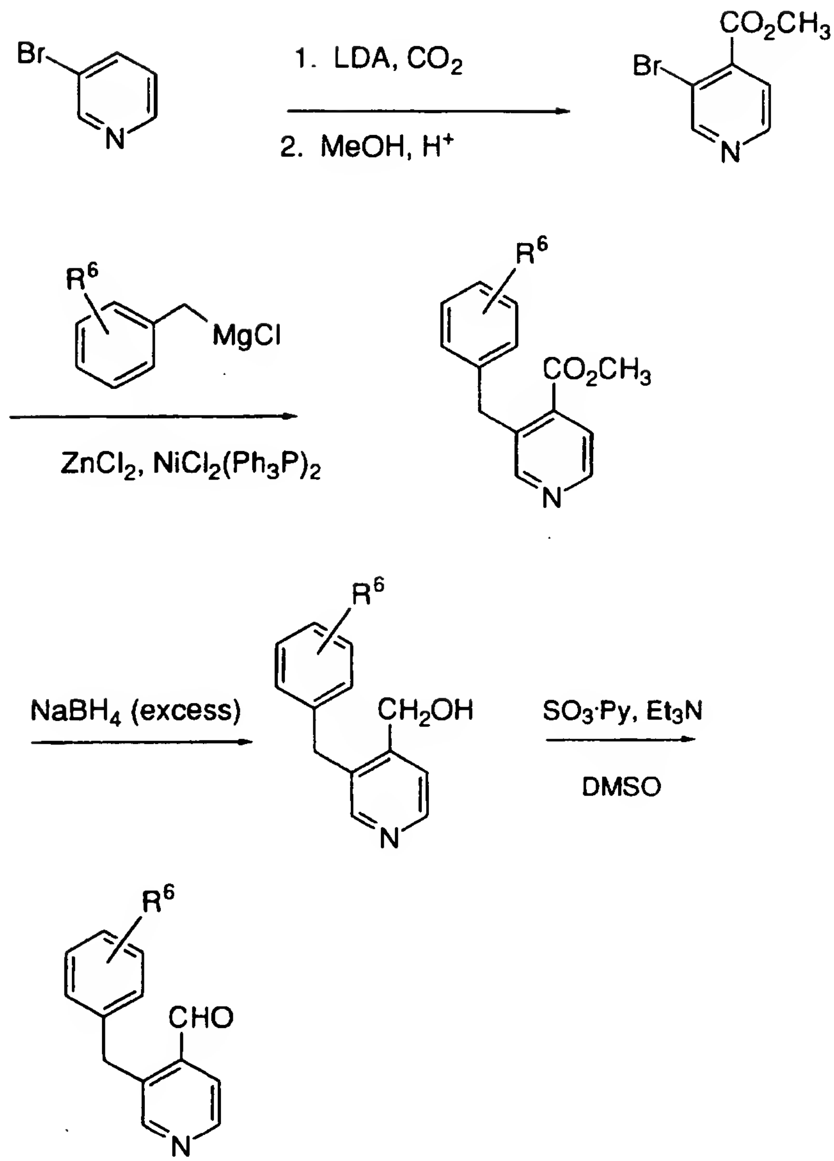


CH3
H2N
N
1) HNO2,Br2
2) KMnO4
3) MeOH, H+
CO2CH3
Br
N
R6
MgCl
ZnCl2,NiCl2(Ph3P)2
R6
CO2CH3
N
NaBH4 (excess)
R6
CH2OH
N
SO3·Py, Et3N
DMSO
R6
CHO
N

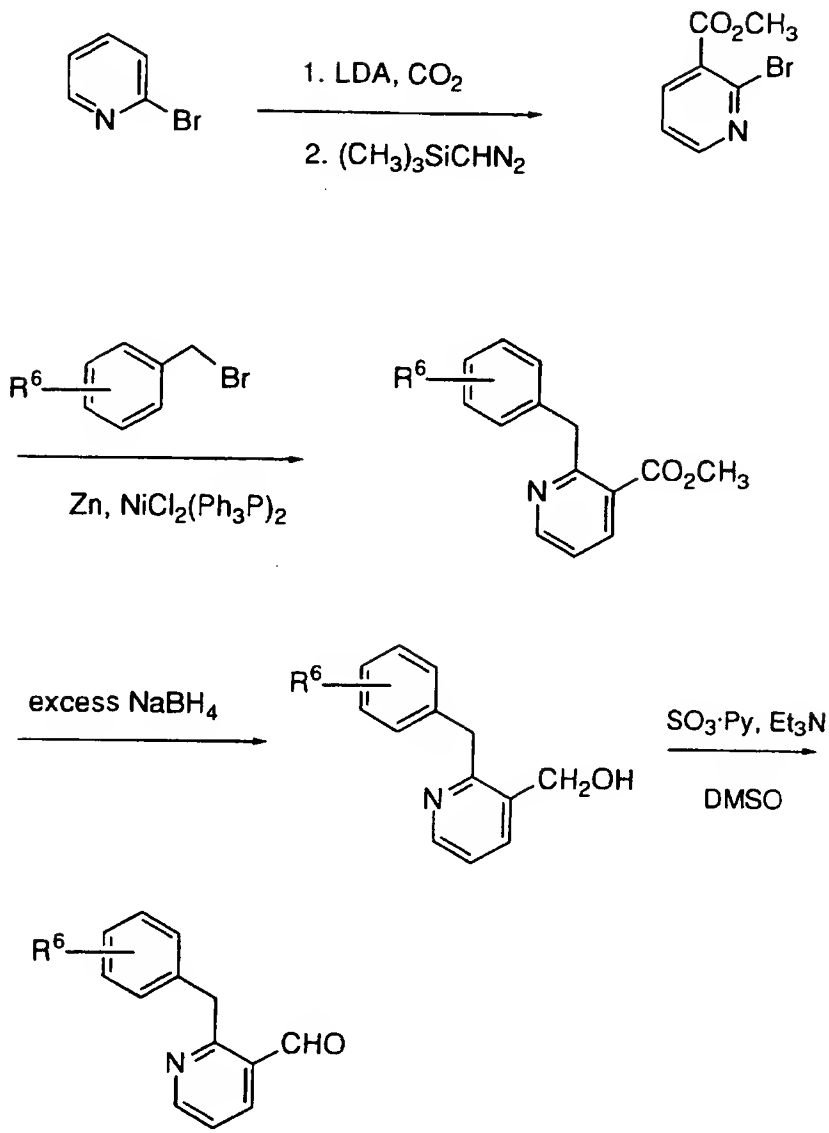
SCHEME 19


1. EtO(CO)Cl
2.
R6
Br
Zn, CuCN
3. S, xylene, heat
CO2CH3
N
NaBH4
(excess)
CH2OH
SO3·Py, Et3N
DMSO
CHO
MgCl
ZnCl2, NiCl2(Ph3P)2

SCHEME 20


Br
N
1. LDA, CO_2
2. MeOH, H^+
CO_2CH_3
Br
N
R^6
MgCl
$ZnCl_2$, $NiCl_2(Ph_3P)_2$
R^6
CO_2CH_3
N
$NaBH_4$ (excess)
R^6
CH_2OH
N
$SO_3 \cdot Py$, Et_3N
DMSO
R^6
CHO
N

SCHEME 21


CO2CH3
Br
N
Br
1. LDA, CO2
2. (CH3)3SiCHN2
R6
Br
Zn, NiCl2(Ph3P)2
CO2CH3
excess NaBH4
CH2OH
SO3·Py, Et3N
DMSO
CHO

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restinosis, polycystic

kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and

quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

Step A: 1-Trityl-4-(4-cyanobenzyl)-imidazole

To a suspension of activated zinc dust (3.57g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon at 20°C. The suspension was cooled to 0°C and a-bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C for 6 hours and bis(triphenylphosphine)Nickel II chloride (2.4g, 3.64 mmol) and 4-iodo-1-tritylimidazole (15.95g, 36.6 mmol, S. V. Ley, et al., J. Org. Chem. **56**, 5739 (1991)) were added in one portion.The resulting mixture was stirred 16 hours at 20°C and then quenched by addition of sat. aq. NH_4Cl solution (100 mL) and the mixture stirred for 2 hours. Saturated aq. $NaHCO_3$ solution was added to give a pH of 8 and the solution was extracted with EtOAc (2 x 250 mL), dried, ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 0-20% EtOAc in CH_2Cl_2 to afford the title compound as a white solid.

^1H NMR ($CDCl_3$, 400MHz) δ 7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s), and 3.93(2H, s)ppm.

Step B: 2-Phenyl-5-methylpyridine

A mixture of 2-bromo-5-methylpyridine (2.00 g, 11.63 mmol), phenylboronic acid (1.56 g, 12.79 mmol), barium hydroxide (5.50g, 17.4 mmol), DME (80 mL) and water (15 mL) was purged with dry argon. Tetrakis(triphenylphosphine)palladium(0) (672 mg, 0.58 mmol) was added, and the resultant solution was stirred at 80°C for 4 hours. The solvents were evaporated in vacuo, and the residue partitioned between EtOAc and water and acidified with 1M aq. HCl. The aqueous extract was separated, and extracted with EtOAc. The organic extracts were combined, washed with $NaHCO_3$ and 5% aq. $Na_2S_2O_3$, dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue was purified by chromatography (Silica gel, CH_2Cl_2) to afford the title compound.
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.52 (1H, s), 7.96(2H, d, J=7.0Hz), 7.63(1H, d, J=8.0Hz), 7.55(1H, brd, J=8.0Hz), 7.50-7.35(3H, m), and 2.37(3H, s) ppm.

Step C: 2-Phenyl-5-carboxypyridine

A suspension of 2-phenyl-5-methyl pyridine (1.03g, 6.09 mmol) and potassium permanganate (2.89g, 18.3 mmol), in water (25 mL) was heated at reflux for 2 hours. The reaction was allowed to cool to ambient temperature and filtered through celite to remove the solids. Acetic acid (1 mL) was added to the colourless filtrate and the product was collected as a white solid by filtration.
^{1}H NMR (CD_3OD, 400MHz) δ 9.18(1H, s), 8.41(1H, dd, 2.2 and 8.2Hz), 8.08-8.02(2H, m), 7.97(1H, dd, J=8.2 and 0.7Hz) and 7.56-7.46(3H, m) ppm.

Step D: 2-Phenyl-5-hydroxymethylpyridine

To a solution of 2-phenyl-5-carboxypyridine (520 mg, 2.61 mmol) in tetrahydrofuran (10 mL) at 0°C was added 1.0 M lithium aluminum hydride in tetrahydrofuran (2.61 mL, 2.61 mmol) over 10 minutes. The reaction was allowed to stir at ambient temperature for 16 hours, cooled to 0°C, and quenched by dropwise

addition of water (0.20 mL), 4 N aq. NaOH (0.20 mL), and water (0.60 mL). The reaction was filtered through a pad of Celite and the filtrate evaporated in vacuo. The residue was chromatographed (silica gel, 0-5% MeOH in CH_2Cl_2) to afford the title compound. ^1H NMR ($CDCl_3$, 400MHz) δ 8.66(1H, s), 7.97(2H, d, J=7.9Hz), 7.82-7.70(2H, m), 7.52-7.38(3H, m), 4.77(2H, s) and 1.89(1H, brs) ppm.

<u>Step E:</u> <u>1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl) imidazole hydrochloride salt</u>

To a solution of 2-phenyl-5-hydroxymethylpyridine (264 mg, 1.43 mmol) and diisopropylethylamine (0.522 mL, 3.00 mmol) in dichloromethane (10 mL) at -78°C was added trifluoromethanesulfonic anhydride (0.252 mL, 1.50 mmol) and the mixture stirred at -78°C for 15 minutes. To this mixture was added a solution of 1-trityl-4-(4-cyanobenzyl)imidazole (608 mg , 1.43 mmol) in dichloromethane (9 mL). The mixture was allowed to warm to ambient temperature and stirred for 16 hours. The solvent was evaporated in vacuo. The residue was dissolved in methanol (15 mL), heated at reflux for 1 hour, and the solvent evaporated in vacuo. The residue was partitioned between dichloromethane and sat. aq. $NaHCO_3$ solution. The organic layer was dried, (Na_2SO_4) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 0-5% NH_4OH in CH_2Cl_2). The amine was converted to the HCl salt by treatment with 1.0M HCl in aqueous acetonitrile. Evaporation of the solvent in vacuo afforded the title compound as a white solid.

FAB MS 351 (MH^+)

^1H NMR (CD_3OD, 400MHz) δ 8.38(1H, d, J=2.4Hz),7.97(2H, m), 7.64(1H, d, J=8.2Hz), 7.60(1H, s), 7.56-7.40(5H, m), 7.28-7.20(1H, m), 7.17(2H, d, J=8.0Hz), 6.97(1H, s), 4.96(2H, s) and 3.89(2H, s) ppm.

<u>EXAMPLE 2</u>

1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl) imidazole hydochloride (66.7mg, 0.159 mmol) was partitioned between CH_2Cl_2 (1mL) and sat. aq. Na_2CO_3 (1 mL). The organic layer was separated, dried, ($MgSO_4$) and the solvent evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL), 3-chloroperbenzoic acid (109 mg, 0.506 mmol) was added and the solution stirred at ambiant temperature for 16 hours. The reaction was partitioned between CH_2Cl_2 (5mL) and sat. aq. Na_2CO_3 (2mL) and the organic layer separated, dried, ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel 4-10% MeOH in CH_2Cl_2). The amine was converted to the HCl salt by treatment with 1.0M HCl in aqueous acetonitrile. Evaporation of the solvent in vacuo afforded the title compound as a white solid. ^{1}H NMR (CD3OD, 400MHz) δ 9.18(1H, s), 8.13(1H,s), 7.80-7.20(12H,m), 5.53(2H,s) and 4.28(2H,s) ppm.

EXAMPLE 3

1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

Step A: 3-Phenyl-6-carboxypyridine

A suspension of 3-phenyl-6-methyl pyridine (1.99g, 11.78 mmol) and potassium permanganate (7.65, 48.6 mmol), in water (50 mL) was heated at reflux for 16 hours. The reaction was allowed to cool to ambient temperature and filtered through celite to remove the solids. Acetic acid (2 mL) was added to the colourless filtrate and the product was collected as a white solid by filtration. ^{1}H NMR (CD3OD, 400MHz) δ 8.86(1H, s), 8.15(2H,m), 7.70(2H,d, J=6.7Hz) and 7.60-7.30(3H,m) ppm.

Step B: 3-Phenyl-6-hydroxymethylpyridine

To a solution of 3-phenyl-6-carboxypyridine (1.05g, 5.27 mmol) in tetrahydrofuran (25 mL) at 0°C was added 1.0 M lithium aluminum hydride in tetrahydrofuran (10.0 mL, 10.0 mmol) over 10 minutes. The reaction was allowed to stir at ambient temperature for 6 hours, cooled to 0°C, and quenched by dropwise addition of water (0.50 mL), 4 N aq. NaOH (0.50 mL), and water (1.5 mL). The reaction was filtered through a pad of Celite and the filtrate evaporated in vacuo. The residue was chromatographed (silica gel, 0-5% MeOH in CH_2Cl_2) to afford the title compound. ^1H NMR ($CDCl_3$, 400MHz) δ 8.79(1H, d, J=1.0Hz), 7.88(1H, dd, J=8.6 and 1.5Hz), 7.58(2H,d, J=6.7Hz), 7.49(2H,t, J=7.0Hz), 7.41(1H,t, J=7.0Hz), 7.33(1H,d, J=7.6Hz), 4.83(2H,s) and 3.75(1H,brs) ppm.

Step C: 1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl) imidazole hydrochloride salt

To a solution of 3-phenyl-6-hydroxymethylpyridine (192 mg, 1.04 mmol) and diisopropylethylamine (0.360 mL, 2.07 mmol) in dichloromethane (8 mL) at -78°C was added trifluoromethanesulfonic anhydride (0.180 mL, 1.07 mmol) and the mixture stirred at -78°C for 1 hour. To this mixture was added a solution of 1-trityl-4-(4-cyanobenzyl)imidazole (441 mg , 1.04 mmol) in dichloromethane (9 mL). The mixture was allowed to warm to ambient temperature and stirred for 4 hours. The solvent was evaporated in vacuo. The residue was dissolved in methanol (10 mL), heated at reflux for 1 hour, and the solvent evaporated in vacuo. The residue was partitioned between dichloromethane and sat. aq. $NaHCO_3$ solution. The organic layer was dried, (Na_2SO_4) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, EtOAc and then 5% MeOH in CH_2Cl_2). The amine was converted to the HCl salt by treatment with 1.0M HCl in aqueous acetonitrile. Evaporation of the solvent in vacuo afforded the title compound as a white solid.

FAB HRMS exact mass calcd for $C_{23}H_{19}N_4$ 351.160972 (MH^+); found 351.161206.
^{1}H NMR (CD3OD, 400MHz) δ 9.20(1H, d, J=1.4Hz), 8.75(1H, d, J=2.2Hz), 8.16(1H, d, J=8.20), 7.66 (2H, d, J=8.4Hz), 7.60-7.40(7H, m), 7.26(2H, d, J=8.0Hz), 5.73(2H, s) and 4.27(2H, s) ppm.
Anal. Calcd. for $C_{23}H_{18}N_4 \cdot 2.00\ HCl \cdot 0.80\ H_2O$:
C, 63.11; H, 4.97; N, 12.80.
Found: C, 63.10; H, 4.97; N, 12.95.

EXAMPLE 4

1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl) imidazole hydochloride (100.0mg, 0.236mmol) was partitioned between CH_2Cl_2 (2mL) and sat. aq. Na_2CO_3 (1mL). The organic layer was separated, dried, ($MgSO_4$) and the solvent evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL), 3-chloroperbenzoic acid (143mg, 0.472 mmol) was added and the solution stirred at ambient temperature for 16 hours. The reaction was partitioned between CH_2Cl_2 (5mL) and sat. aq. Na_2CO_3 (2mL) and the organic layer separated, dried, ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel 4-10% MeOH in CH_2Cl_2The amine was converted to the HCl salt by treatment with 1.0M HCl in aqueous acetonitrile. Evaporation of the solvent in vacuo afforded the title compound as a white solid.
^{1}H NMR free base (CDCl3, 400MHz) δ 8.44(1H, d, J=1.5Hz), 7.63(1H,s), 7.60-7.20(10H,m), 7.03(1H,s), 6.35(1H,d, J=8.2Hz), 5.29(2H,s) and 3.96(2H,s) ppm.

EXAMPLE 5

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

Step A: 2-(3-Trifluoromethoxyphenyl)-5-methylpyridine

To a solution of 3-bromotrifluoromethoxybenzene (0.590mL, 4.00 mmol) in THF (12 mL) at -78°C was added t-butyl lithium (4.71mL, of a 1.7M solution in pentane, 8.00 mmol. After 10 minutes zinc chloride(4.0mL, of a 1M solution in diethylether, 4.00 mmol) was added. The reaction was stirred for 10 minutes at -78°C and then allowed to warm to 0°C and stirred for 30minutes. This solution was added via cannula to a solution of 2-bromo-5-methyl pyridine and bis(triphenylphosphine) Nickel II chloride. The reaction stirred for 1 hour at 0°C and then at ambient temperature for a furthur 1 hour. Saturated ammonium hydroxide solution (3 mL) was added and the mixture stirred until homogenous, extracted with Et_2O and the organic extracts washed with saturated brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed (Silica gel, 25-50% CH_2Cl_2 in hexanes).
^1H NMR (CD_3OD, 400MHz) δ 8.48(1H, s),7.93(1H, brd, J=8.0Hz), 7.87(1H, s), 7.79(2H, d, J=8.0Hz), 7.74(2H, d, J=8.0Hz), 7.56(1H, t, J=8.0Hz), 7.32(1H, brd, J=8.0Hz) and 2.40(3H, s) ppm.

Step B: 2-(3-Trifluoromethoxyphenyl)-5-carboxy pyridine

A solution of 2-(3-Trifluoromethoxyphenyl)-5-methylpyridine (2.35g, 2.22 mmol) and tetrabutylammonium permanganate (1.904, 0.012mol), in pyridine (8 mL) was heated at 75°C for 16 hours. The cooled reaction was filtered through celite to remove the solids. The solid was washed with EtOAc and MeOH and the filtrate evaporated in vacuo to afford the title compound of sufficient purity to be used in the next step.

Step C: 2-(3-Trifluoromethoxyphenyl)-5-hydroxymethylpyridine

To a solution of 2-(3-trifluoromethoxyphenyl)-5-carboxy pyridine (2.0 g, 7.06 mmol) in tetrahydrofuran (15 mL) at 0°C was added 1.0 M lithium aluminum hydride in tetrahydrofuran

(7.07 mL, 7.07 mmol) over 10 minutes. The reaction was allowed to stir at ambient temperature for 4 hours, cooled to 0°C, and quenched by dropwise addition of saturated Na_2SO_4 (1.0 mL). The reaction was diluted with diethylether, filtered through a pad of Celite and the filtrate evaporated in vacuo. The residue was chromatographed (silica gel, 50% EtOAc in hexanes) to afford the title compound.

^{1}H NMR (CD3OD, 400MHz) δ 8.62(1H, d, J=1.0Hz), 8.00-7.84(H,m), 7.57(1H, t, J=8.0Hz), 7.33(1H,brd, J=8.0Hz) and 4.84(2H,s) ppm.

Step D: 1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

To a solution of 2-(3-trifluoromethoxyphenyl)-5-hydroxymethylpyridine (66 mg, 0.25 mmol), diisopropylethylamine (0.085 mL, 0.49 mmol), and 1-trityl-4-(4-cyanobenzyl)imidazole (105 mg , 0.25 mmol) in dichloromethane (1.4 mL) at -78°C was added trifluoromethanesulfonic anhydride (0.041 mL, 0.25 mmol) and the mixture stirred at -78°C for 1 hour. The reaction was allowed to warm to ambient temperature and stirred for 4 hours. The solvent was evaporated in vacuo. The residue was dissolved in methanol (15 mL), heated at reflux for 1 hour, and the solvent evaporated in vacuo. The residue was partitioned between dichloromethane and sat. aq. Na_2CO_3 solution. The organic layer was dried, (Na_2SO_4) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 3% MeOH in CH_2Cl_2). The amine was converted to the HCl salt by treatment with 1.0M HCl in aqueous acetonitrile. Evaporation of the solvent in vacuo afforded the title compound as a white solid.

^{1}H NMR (CD3OD, 400MHz) δ 9.23(1H, s), 8.67(1H,s), 8.18-8.04(2H, m), 8.00-7.90(2H,m), 7.74(1H, t, J=7.9Hz), 7.62-7.50(4H, m), 7.31(2H, d, J=7.9Hz), 5.71(2H, s), 4.29(2H, s) ppm.

FAB HRMS exact mass calcd for $C_{24}H_{18}N_4OF_3$ 435.143271 (MH^+); found 435.144474.

Anal. Calcd. for $C_{24}H_{17}N_4OF_3 \cdot 2.00\ HCl$:
C, 56.82; H, 3.77; N, 11.04.
Found: C, 56.50; H, 3.88; N, 10.86.

EXAMPLE 6

1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

Step A: 2-(2-Trifluoromethylphenyl)-5-methylpyridine

To a solution of 2 bromo-5-methyl pyridine (1.81g, 10.53 mmol) and barium hydroxide (4.97 g, 15.78 mmol) in water (15 mL) was added DME (80 mL). This mixture was treated sequentially with 2-(trifluoromethyl)phenylboronic acid (2.00g, 10.53 mmol) and palladium tetrakis(triphenylphosphine) (553 mg, 0.48 mmol) and the mixture warmed to 80°C for 48 hours. Water (100mL) was added and the pH of the solution was adjusted to 10 and extracted with EtOAc (3X200mL).

The organic extracts were combined, washed with brine, dried (MgSO4), and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 50% -100% CH_2Cl_2 in hexanes) to afford the title compound.

^1H NMR (CDCl3, 400MHz) δ 8.52(1H, s), 7.75(1H, d, J=7.9Hz), 7.64-7.44(4H, m), 7.32(1H, d, J=7.9Hz) and 2.40(3H,s) ppm.

Step B: 2-(2-Trifluoromethylphenyl)-5-carboxypyridine

A suspension of 2-(2-Trifluoromethylphenyl)-5-methylpyridine (0.40g, 1.68 mmol) and potassium permanganate (1.60g, 10.1 mmol), in water (10 mL) was heated at reflux for 16 hours. The reaction was filtered hot through celite to remove the solids. Acetic acid was added to the colourless filtrate to yield a pH of 5 and the resulting suspension was extracted with CH_2Cl_2.washed

with water (10 mL), dried, ($MgSO_4$), and the solvent evaporated in vacuo to afford the title compound.
^{1}H NMR (CD_3OD, 400MHz) δ 9.34(1H, s), 8.41(1H,d, J=8.2Hz), 7.80(1H,d, J=7.9Hz) and 7.70-7.50(4H,m) ppm.

Step C: 2-(2-Trifluoromethylphenyl)-5-hydroxymethylpyridine

To a solution of 2-(2-Trifluoromethylphenyl)-5-carboxypyridine (220 mg, 1.23 mmol) in tetrahydrofuran (10 mL) at 0°C was added 1.0 M lithium aluminum hydride in tetrahydrofuran (1.23 mL, 1.23 mmol) over 10 minutes. The reaction was allowed to stir at ambient temperature for 16 hours, cooled to 0°C, and quenched by dropwise addition of water (0.05 mL), 2.5 N aq. NaOH (0.05 mL), and water (0.15 mL). Sodium sulfate was added, the reaction filtered through a pad of Celite and the filtrate evaporated in vacuo. The residue was chromatographed (silica gel, CH_2Cl_2 then EtOAc) to afford the title compound.
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.63(1H, s), 7.80-7.40(6H,m) and 4.77(2H, s) ppm.

Step D: 1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

The title compound was prepared using the procedure described for Example 5, step D using 2-(2-trifluoromethylphenyl)-5-hydroxymethylpyridine from Step C in place of 2-(3-trifluoromethoxyphenyl)-5-hydroxymethylpyridine.
^{1}H NMR (CD_3OD, 400MHz) δ 9.17(1H, s), 8.42(1H,s), 8.00-7.40(11H, m), 5.60(2H, s), 4.26(2H, s) ppm.
FAB MS 419 (MH^+)
Anal. Calcd. for $C_{24}H_{17}N_4F_3 \cdot 2.95$ HCl. 0.6 EtOAc:
C, 54.78; H, 4.31; N, 9.68.
Found: C, 54.79; H, 4.18; N, 9.68.

EXAMPLE 7

1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

Step A: 3-Phenyl-6-methylpyridine N-oxide

A solution of 3-phenyl-6-methyl pyridine (2.36g, 13.95 mmol), in CH_2Cl_2 (40 mL) at 0°C was treated with MCPBA (3.58g, 13.95 mmol) for 1 hour. Saturated aq. Na_2CO_3 (50 mL) was added and the reaction was extracted with CH_2Cl_2 (20 mL). The organic extracts were dried ($MgSO_4$), and the solvent evaporated in vacuo to afford the title compound.

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.53(1H, s), 7.60-7.20(7H, m) and 2.57(3H, s) ppm.

Step B: 3-Phenyl-2-chloro-6-methylpyridine and 3-phenyl-4-chloro-6-methylpyridine

A solution of 3-phenyl-6-methyl pyridine-N-Oxide (1.42g, 7.66 mmol), in P_2O_5 (50 mL) at 0°C was at 80°C for 3 hours. The reaction was allowed to cool to room temperature and then poured over ice (400g). Saturated aq. Na_2CO_3 was added until the pH of the solution was 8 and the reaction was extracted with CH_2Cl_2 (3X250 mL). The organic extracts were dried ($MgSO_4$), and the solvent evaporated in vacuo. The residue was chromatographed (silica gel, 10-20% EtOAc in CH_2Cl_2 to afford 3-Phenyl-2-chloro-6-methylpyridine (First eluted)

^{1}H NMR ($CDCl_3$, 400MHz) δ 7.56(1H, d, J=7.6Hz), 7.60-7.30(5H,m), 7.15(1H,d, J=7.6Hz) and 2.59(3H, s) ppm.

3-Phenyl-4-chloro-6-methylpyridine (Second eluted).

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.43(1H, s), 7.60-7.40(5H,m), 7.29(1H,s) and 2.59(3H, s) ppm.

Step C: 3-Phenyl-2-chloro-6-bromomethylpyridine

A solution of 3-Phenyl-2-chloro-6-methylpyridine (0.094g, 0.462 mmol), NBS (0.086g, 0.485 mmol) and AIBN (0.008g, 0.046mmol) in CCl_4 (3 mL) were heated at reflux for

2 hours. The solvent was evaporated and the residue chromatographed(Silica gel, 100% CH_2Cl_2 to afford the title compound. ^1H NMR (CDCl3, 400MHz) δ 7.68(1H, d, J=7.6Hz), 7.60-7.40(6H,m), and 4.56(2H, s) ppm.

Step D: 1-(3-Phenyl-2-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

To 1-trityl-4-(4-Cyanobenzyl)-imidazole (88.4mg, 0.208 mmol) in acetonitrile (1 mL) was added 3-phenyl-2-chloro-6-bromomethylpyridine (53.5mg, 0.189 mmol) and the mixture heated at 65°C for 16 hours. The residue was dissolved in methanol (3 ml) and heated at reflux for 2 hours, cooled and evaporated to dryness. The residue was partitioned between sat. aq. Na_2CO_3 solution and CH_2Cl_2. The organic layer was dried, ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 2.5-3% MeOH in CH_2Cl_2) to afford the free base which was converted to the HCl salt by treatment with one equivalent of HCl in aqueous acetonitrile. Evaporation of solvent in vacuo afforded the title compound as a white powder.

^1H NMR (CD3OD, 400MHz) δ 9.11(1H, s), 7.64(1H.d, J=7.7Hz), 7.55(2H,d, J=8.2Hz), 7.51(1H,s), 7.50-7.34(5H,m), 7.32-7.20(3H, m), 5.56(2H, s), 4.27(2H, s) ppm.

Anal. Calcd. for $C_{23}H_{17}ClN_4 \cdot 1.00$ HCl. 0.6 EtOAc:
C, 54.78; H, 4.31; N, 9.68.
Found: C, 54.79; H, 4.18; N, 9.68.

EXAMPLE 8

1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

The title compound was prepared using the procedure described for Example 7, steps C and D using 3-phenyl-4-chloro-6-methylpyridine in place of 3-phenyl-6-methyl pyridine.

Anal. Calcd. for $C_{24}H_{17}N_4$ Cl·1.00 HCl. 0.30 H2O:
C, 64.74; H, 4.39; N, 13.13.
Found: C, 64.82; H, 4.52; N, 12.93.

EXAMPLE 9

1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

Step A: 2-Amino-3-Phenyl-6-methylpyridine

A solution of 3-phenyl-6-methyl pyridine (0.815 g, 4.82 mmol), and sodium amide (752mg, 19.3mmol) in diethylaniline (10mL) was heated at 180°C for 72 hours. The reaction was cooled and quenched with ice (100g), and the mixture extracted with EtOAc. The organic extract was washed with brine (50 mL) , dried ($MgSO_4$), silica gel (100g) was added and the solvent evaporated in vacuo.

The material was loaded onto a column and chromatographed (Silica gel, eluting with 0-100% EtOAc in CH_2Cl_2) to afford the title compound.

^{1}H NMR (CDCl3, 400MHz) δ 7.50-7.20(6H, m) 6.61(1H,d, J=7.0Hz), and 2.42(3H, s) ppm.

Step B: N-bis t-Butoxycarbonyl-2-Amino-3-Phenyl-6-methylpyridine

A solution of 2-amino-3-phenyl-6-methyl pyridine (1.21 g, 6.57 mmol), di t-butylcarbonate(3.58g, 16.4 mmol), triethylamine (2.29 mL, 16.4 mmol) and DMAP (0.803g, 6.57 mmol) in CH_2Cl_2 (20mL) were heated at 65°C for 16 hours. The reactionwas diluted with sat. aq. Na_2CO_3 and extracted with CH_2Cl_2. The solvent was evaporated in vacuo. and the residue chromatographed (Silica gel, eluting with 20% EtOAc in CH_2Cl_2) to afford the title compound. ^1H NMR (CDCl3, 400MHz) δ 7.62(1H, d, J=7.7Hz), 7.41-7.30(5H, m), 7.19(1H, d, J=7.7Hz), 2.59(3H, s) and 1.28(18H, s) ppm.

Step C: 2-(bis t-butoxycarbonylamino)-3-phenyl-6-methylpyridine-N-oxide

A solution of N-bis t-butoxycarbonyl-2-amino-3-phenyl-6-methylpyridine (0.215g, 0.56 mmol), in CH_2Cl_2 (4 mL) at 0°C was treated with MCPBA (0.220g , 0.727 mmol) for 1 hour. Saturated aq. Na_2CO_3 (50 mL) was added and the reaction was extracted with CH_2Cl_2 (2X50 mL). The organic extracts were dried ($MgSO_4$), and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, eluting with 100% EtOAc to afford the title compound. ^1H NMR (CDCl3, 400MHz) δ 7.44-7.36(6H,m), 7.13(1H, d, J=7.7Hz), 2.56(3H, s) and 1.31(18H, s) ppm.

Step D: N-bis t-Butoxycarbonyl-2-amino-3-phenyl-6-acetoxymethylpyridine

A solution of 2-(bis t-butoxycarbonylamino)-3-phenyl-6-methylpyridine-N-oxide (0.223g, 0.557 mmol), in acetic anhydride (5 mL) was heated at 65°C for 24 hours. The solvent was evaporated in vacuo and the residue chromatographed (30-50%EtOAc in hexanes) to afford the title compound.
^1H NMR (CDCl3, 400MHz) δ 7.74(1H, d, J=7.7Hz), 7.50-7.30(6H, m), 5.25(2H, s), 2.17(3H, s) and 1.28(18H, s) ppm.

Step E: N-bis t-Butoxycarbonyl-2-amino-3-phenyl-6-hydroxymethylpyridine

A solution of 2-(bis t-butoxycarbonylamino)-3-phenyl-6-acetoxymethylpyridine (0.040g, 0.09 mmol), THF (1.3 mL) was treated with Lithium hydroxide (1M solution in water 0.271 ml, 0.271 mmol) at room temperature for 16 hours. The reaction was diluted with water and extracted with CH_2Cl_2. The organic extracts were dried ($MgSO_4$),and the solvent evaporated in vacuo to afford the title compound.
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.74(1H, d, J=7.8 Hz), 7.44-7.33(5H, m), 7.31(1H,brd, J=7.8Hz), 4.81(2H, s), and 1.29(18H, s) ppm.

Step F: 1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

The title compound was prepared using the procedure described for Example 3 step C using N-bis t-butoxycarbonyl-2-amino-3-phenyl-6-hydroxymethylpyridine in place of 3-phenyl-6-hydroxymethyl-pyridine. In this case the free base was treated with TFA and triethylsilane to effect cleavage of the t-butoxycarbonyl groups which was followed by its conversion to the hydrochloride salt.
^{1}H NMR (CD_3OD, 400MHz) δ 9.23(1H, s), 7.80-7.20(H, m), 6.96(1H,s), 6.65(1H,d, J=7.6Hz), 5.66(2H, s), 4.33(2H, s) ppm.
Anal. Calcd. for $C_{23}H_{19}N_5 \cdot 1.00$ HCl. 0.95 H2O 0.35 EtOAc:
C, 60.26; H, 5.33; N, 14.40.
Found: C, 60.04; H, 5.10; N, 14.45.

EXAMPLE 10

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 µl

containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compound of the instant invention described in the above Examples 1-9 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC_{50} of ≤50 μM.

EXAMPLE 11

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75%

confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 12

In vivo growth inhibition assay

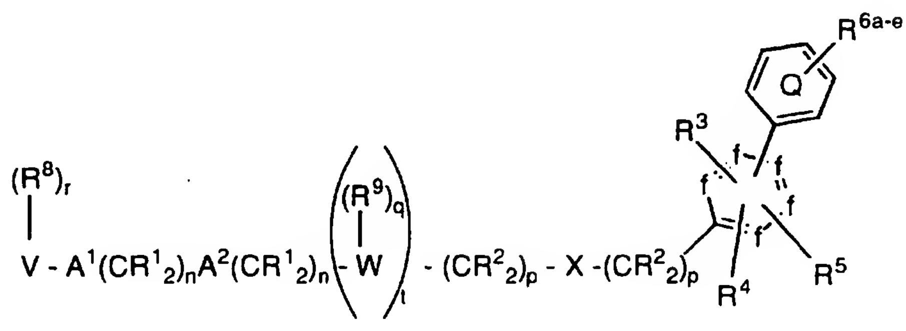
To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in

a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photo-micrographs are taken 16 days after the cultures are seeded and comparisons are made.

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



A

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 and R^2 are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

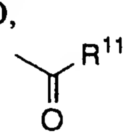
c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, $-CH=CH-CH_2-$, $-(CH_2)_4-$ and $-(CH_2)_3-$;

provided that when R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 

,
f) $-SO_2R^{11}$,
g) $N(R^{10})_2$ or
h) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,
b) aryl, substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br,

$R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^9 is independently selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{11}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^7C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^7C(O)-, -NR^7-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$- or -$S(=O)_m$-;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

p is independently 0, 1, 2, 3 or 4;

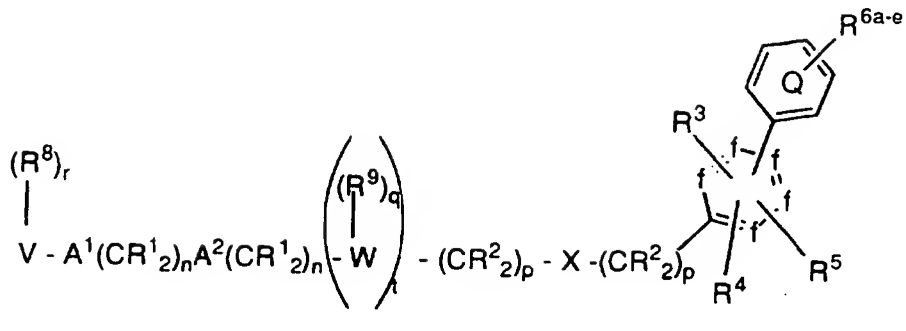
q is 0, 1, 2 or 3;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 of the formula A:



A

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is independently selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-,

$R^{10}{}_2N-C(NR^{10})-$, CN, NO_2, $R^{10}C(O)-$, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

c) unsubstituted C_1-C_6 alkyl;

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}{}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)-NR^{10}-$;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}{}_2N-C(NR^{10})-$, CN, NO_2, $R^{10}C(O)-$, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

c) unsubstituted C_1-C_6 alkyl;

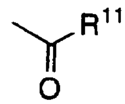
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}{}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)-NR^{10}-$; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered

heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 

,

f) $-SO_2R^{11}$,
g) $N(R^{10})_2$ or
h) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,
b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^9 is selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{11}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-,

CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

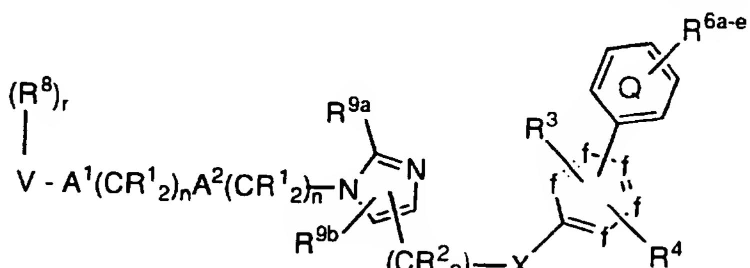
W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

X is a bond, O, -C(=O)-, -CH=CH-, -C(O)NR^7-, -NR^{7}C(O)-, -NR^7-, -S(O)2N(R^{10})-, -N(R^{10})S(O)2- or -S(=O)m-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the formula B:



B

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R1 is selected from: hydrogen, C3-C10 cycloalkyl, R^{10}O-, -N(R^{10})2, F or C1-C6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;
provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

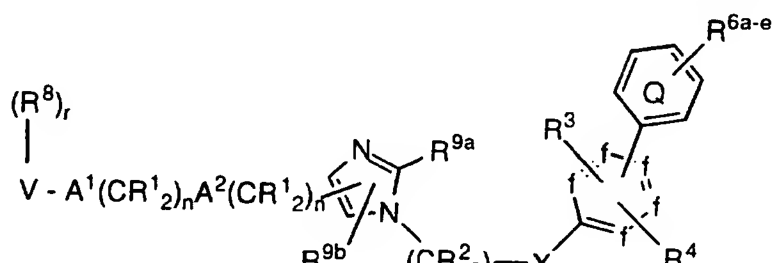
X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and

r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the formula C:



C

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

provided that when V is heterocycle, attachment of V to R^8 and to A^1 is through a substitutable ring carbon;

X is a bond, -CH=CH-, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-NR^{10}-$, O or -C(=O)-;

m is 0, 1 or 2;

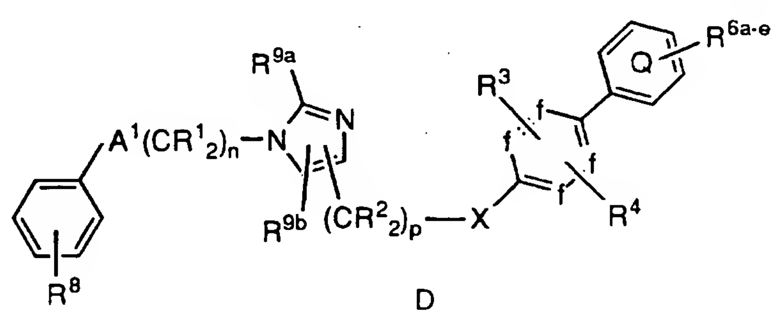
n is independently 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O; and

r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 3 of the formula D:



D

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$, F or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

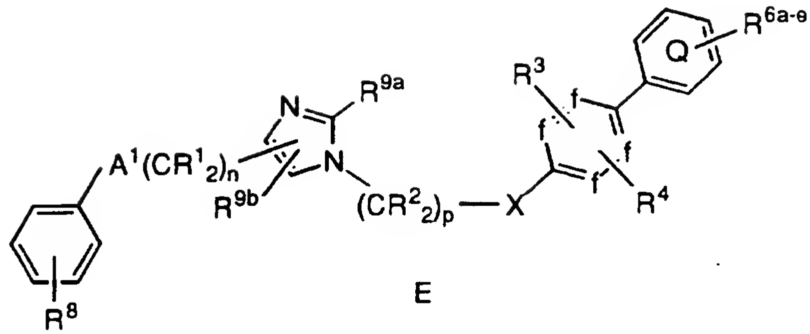
A^1 is selected from: a bond, -C(O)-, O, -$N(R^{10})$-, or $S(O)_m$;

X is a bond, -CH=CH-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, -NR^{10}-, O or -C(=O)-,

n is	0 or 1; provided that n is not 0 if A^1 is a bond, O, -$N(R^{10})$- or $S(O)_m$;
m is	0, 1 or 2; and
p is	0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 4 of the formula E:



E

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:
- a) hydrogen,
- b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,
- c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:
- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
- c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl

ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

provided that when R^8 is heterocycle, attachment of R^8 to V is through a substitutable ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

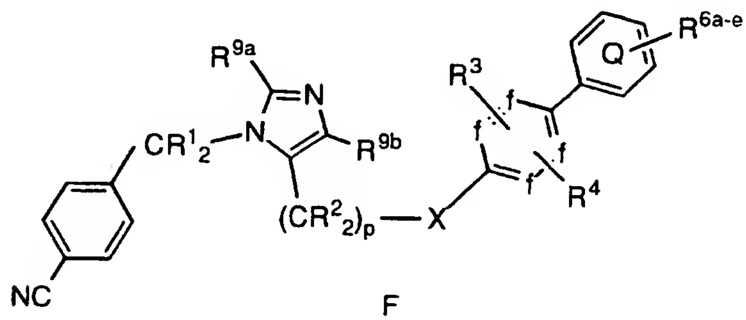
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, -NR^{10}-, O or -C(=O)-;

n is 0 or 1;
m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;

or a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 5 of the formula F:



F

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or F,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3,

R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

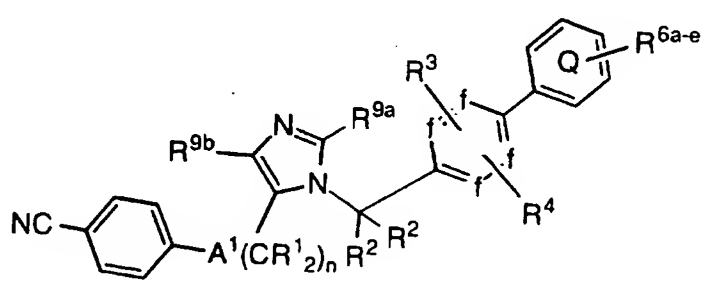
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary1, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-NR^{10}-$, O or -C(=O)-;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 6 of the formula G:



G

wherein:

from 1-2 of f(s) are independently N or N->O, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle or C_3-C_{10} cycloalkyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

provided that when R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} is unsubstituted or substituted heterocycle, attachment of R^3, R^{6a}, R^{6b}, R^{6c}, R^{6d} or R^{6e} to the 6-membered heteroaryl ring, or phenyl ring respectively, is through a substitutable heterocycle ring carbon;

R^{9a} and R^{9b} are independently hydrogen, halogen, CF_3 or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterаryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or $S(O)_m$;

m is 0, 1 or 2; and
n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

9. A compound which inhibits farnesyl-protein transferase which is:

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

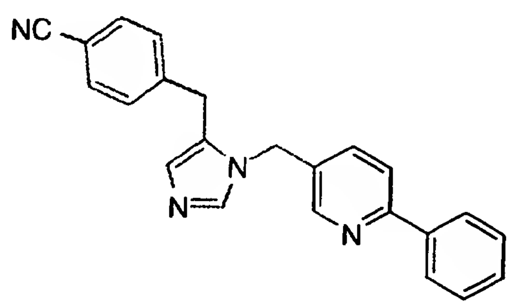
1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
or

1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 9 which is:

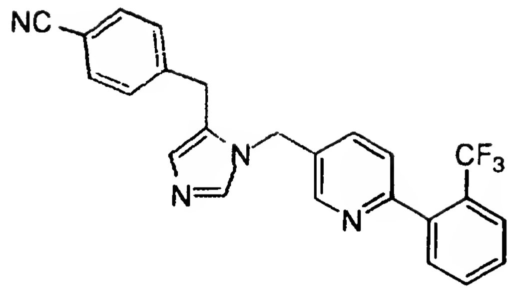
1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole



or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 9 which is:

1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole



or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

13. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

14. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 4.

15. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 9.

16. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

17. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

18. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 14.

19. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

20. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

21. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

22. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 14.

23. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

24. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

25. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

26. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

27. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

28. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

29. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

30. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05304

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 417/00; A61K 31/44
US CL :546/272.7; 514/341

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/272.7; 514/341

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,713,387 A (WATANABE ET AL.) 15 December 1987, see entire document.	1-15
A	US 5,428,164 A (THURKAUF ET AL.) 27 June 1995, see entire document.	1-15
A, P	US 5,587,390 A (SALIMBENI ET AL.) 24 December 1996, see entire document.	1-15
A, E	US 5,633,376 A (THURKAUF ET AL.) 27 May 1997, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
11 JULY 1997

Date of mailing of the international search report
05 AUG 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
FLOYD D. HIGEL
Telephone No. (703) 308-1235

B. FIELDS SEARCHED
Documentation other than minimum documentation that are included in the fields searched:

CHEMICAL ABSTRACTS
CURRENT ABSTRACTS OF CHEMISTRY
INDEX CHEMICUS